SOME SYNTHETIC APPLICATIONS OF BENZOTRIAZOLE METHODOLOGY

BY

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This research work is dedicated to the Uyghur people who suffer under the oppression of the Chinese Government in my homeland, East Turkestan.

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Abstract of Dissertation Presented to the Graduate School
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Requirements for the Degree of Doctor of Philosophy

SOME SYNTHETIC APPLICATIONS OF BENZOTRIAZOLE METHODOLOGY

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May 2002

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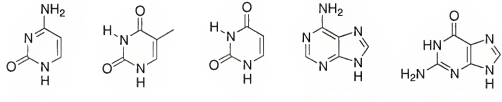
Benzotriazole as a new synthetic auxiliary offers many synthetic advantages in method development for the synthesis of heterocyclic compounds that are of biological importance. Chapter 2 discusses the development of a convenient one-pot synthesis of 5-arylamino-2,4-diarylthiazoles; the desired products are obtained in moderate-to-good yields. Chapter 3 discusses the conversion of 1-alkylbenzotriazoles into the corresponding 3-alkylbenzotriazole 1-oxides, and of 2-alkylbenzotriazoles into the corresponding 2-alkyl-*trans*-4,5,6,7-diepoxy-4,5,6,7-tetrahydrobenzotriazoles in good yields by dimethyldioxirane. Chapter 4 discusses the efficient conversion of substituted vinylbenzotriazoles into benzotriazolyl epoxides by dimethyldioxirane, and the reactions of these epoxides. Chapter 5 discusses the synthesis of 2-benzotriazolylmethyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine via $AlCl_3$ mediated intramolecular cyclization of *N,N*-bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)-3-phenyl-1-propanamine, subsequent nucleophilic substitution of the benzotriazolyl group, and extension of this methodology to the

syntheses of 5,6,7,13b-tetrahydro-9*H*-isoindolo[1,2-*a*][2]benzazepin-9-one and 1,2,5,6,7,11b-hexahydro-3H-pyrrolo[2,1-*a*][2]benzazepin-3-one. Chapter 6 discusses the synthesis of *N*-cycloalkenyl-azoles, a rare class of compounds, via elimination of benzotriazole or 5-phenyltetrazole from the corresponding 1-[1-(heterocycyl)cycloalkyl]-benzotriazoles or [1-(heterocycyl)cycloalkyl]-5-phenyltetrazoles.

CHAPTER 1
GENERAL INTRODUCTION

Heterocyclic compounds are ubiquitous in nature and are essential to life. Genetic material DNA is also composed of heterocyclic bases-pyrimidine and purines. A large number of heterocyclic compounds, both synthetic and natural, are pharmacologically active and are in clinical use. Numerous heterocyclic compounds have applications in agriculture as insecticides, fungicides, herbicides, pesticides etc. Heterocycles has also found applications as sensitizers, developers, antioxidants, and copolymers. They are employed as vehicles in the synthesis of other organic compounds.

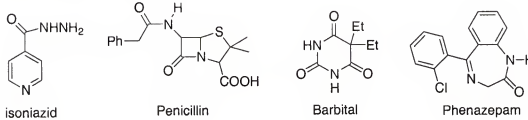
Heterocyclic compounds are important in understanding of the origin of life and interpreting the genetic code of living systems, which is encrypted in the huge deoxyribonucleic acid (DNA) molecules. Nobel Prize winners Watson and Crick demonstrated that derivatives of the well-known nitrogen heterocycles pyrimidine and purine participate directly in the encoding of all genetic information: cytosine, thymine, uracil, adenine and guanine [1997MI38] (Scheme 1-1).



Scheme 1-1

The majority of known pharmaceuticals are heterocycles in nature. For hundreds of years, cure for diseases were obtained from natural sources as leaves, fruits, barks and

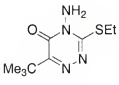
herbs in the way of traditional treatment without realizing the presence of various heterocyclic compounds. Major ingredients of tea, coffee and cocoa are caffeine, threobromine and theophylline. These alkaloids are stimulants of the central nervous systems and can exert diverse effects on the other organ systems. Another type of alkaloid, morphine is well-known painkiller and sometimes used as an adjunct in cancer chemotherapy. Infectious diseases such as tuberculosis were treated successfully using isoniazid, hydrazide of isonicotinic acid (Scheme 1-2). Heterocyclic derivatives of sulfanilamides are much more efficient than that of without heterocyclic fragment against infectious diseases. Important antibiotic Penicillin has a condensed heterocyclic system composed of a five-membered thiazole ring and a four membered azetidine nucleus in the form of β-lactam (Scheme 1-2). Synthetic heterocycles barbiturates and phenazepam (Scheme 1-2) are clinically used as tranquilizers [1997MI145]. There are many more examples of heterocyclic compounds being used as drug, which are extremely important for the well being of human race.



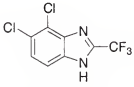
Scheme 1-2

With limited cultivatable land, the ever-increasing population in the world requires dramatic improvements in the productivity of modern agriculture. Pests such as rodents, insects, microorganisms and weeds presently destroy almost half of all the food. Chemical pest control using pesticides and rodenticides is the main approach in plant and crop protection. Regulators of plan growth and development are also of significant

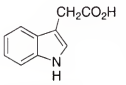
importance in improving harvest. Heterocyclic compounds, especially azines and azoles such as ethiozin and chlorflurazole (Scheme 1-3), are frequently used as herbicides; indole-3-ylacetic acid (heteroauxin) and cytokinins (Scheme 1-3) are used as plant growth regulators to obtain high harvests [1997MI167]. These are a few examples of applications of heterocyclic compounds in agriculture.



Ethiozin



Chlorflurazole



Heteroauxin

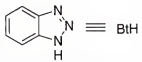
cytokinins

Scheme 1-3

Heterocycles have become indispensable in the recent far-reaching developments in science and technology for numerous applications, including material science, electronics, communications, and aerospace technology; at the same time they remain enormously important in dye and photographic industries, the traditional branches of industry. Synthetic heterocycles have been found to generate laser radiation that offers significant advantage over solid and gas lasers. Heat resistant materials have become essential in the modern world for production of fireproof clothing for fireman, pilots and astronauts. These thermostable compounds are composed of polymers containing aromatic and heteroaromatic residues. For example, fire retardant has been made from polybenzimidazoles and polyquinoxalines compound. Development of heat resistant fibers has significant influence in the progress of aerospace and aeronautics technology. Heterocyclic compounds are utilized in many other ways: liquid crystals, polymeric materials, rubber stabilizers, and vulcanization accelerators.

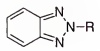
Heterocyclic compounds are important, not only because of their abundance, but above all because of their chemical, biological and technical significance. Thus, synthesis of heterocyclic compounds has vital importance in social and technological advances. This thesis is part of a mission to develop new ways to make carbon-carbon, carbon-heteroatom bond forming reactions, develop new and reliable methodologies to make heterocyclic compounds faster and easier, to simplify the existing processes, and to make them cost effective.

Over the past years, our research group has been involved in the chemistry of benzotriazole as a new synthetic auxiliary offering many synthetic advantages. Benzotriazole (**1.1**, Scheme1-4) is an inexpensive, stable compound. It is soluble in many common organic solvents such as ethanol, benzene, toluene, chloroform, and DMF. It is somewhat soluble in water, but highly soluble in a basic solution that allows for its removal at the end of a synthetic sequence [1998CRV409]. Benzotriazole derivatives are UV-active and thus can be easily monitored by TLC during the reaction; they are crystalline in many cases and can usually be purified using column chromatography.



1.1, Benzotriazole

1.2. Bt^1-R

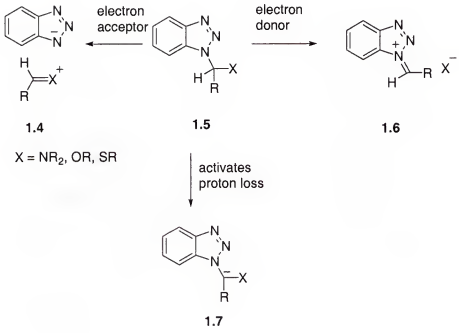


1.3, Bt^2-R

Scheme 1-4

Other interesting aspects of benzotriazole chemistry are that the benzotriazole group behaves [1998CRV409] as (i) a good leaving group, (ii) an activator of CH-bond towards proton loss, (iii) an electron donor, and (iv) a radical precursor [1997JOC1125], [2001H301]. This versatility helps benzotriazole-substituted compounds to perform cationic, anionic and radical reactions.

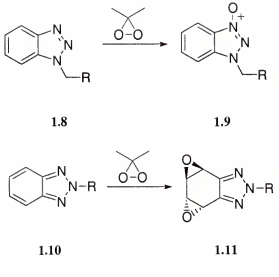
N-Substituted benzotriazoles can exist as either the benzotriazol-1-yl (**1.2**, Bt^1) or benzotriazol-2-yl (**1.3**, Bt^2) isomer. These two isomers are of the same order of stability and show similar reactivity. Because benzotriazole possesses both electron-donor and electron-acceptor properties, compounds with an α heteroatom (N, O, and S) attached to a benzotriazole nitrogen can ionize in two ways: either to form the benzotriazole anion and an imonium, oxonium, or thionium cation **1.4**, or to ionize off the heteroatom substituent to give **1.6** (Scheme 1-5).



Scheme 1-5

Benzotriazole can activate the α-H in **1.5** toward proton loss [1994LA1] to form anion **1.7**, which can react with electrophiles. These properties were used in syntheses of thiazole derivatives in Chapters 2, and substituted epoxides in Chapter 4. When there is a nitrogen atom at the α position, benzotriazole can act as an electron acceptor in **1.5** to form an imonium cation **1.4** and a benzotriazole anion by which benzotriazole can be substituted. This property was utilized in the syntheses of benzazepines in Chapter 5.

When there is no α heteroatom, benzotriazole does not leave easily, and this limits the scope and the utility of benzotriazole methodology. In Chapter 3, we attempted to improve the leaving ability of benzotriazole by converting 1-alkylbenzotriazoles **1.8** to the corresponding *N*-oxides **1.9** using dimethyldioxirane [1997T8643] (Scheme 1-6). Although a successful methodology has been developed to oxidize 1-alkylbenzotriazoles, the leaving ability of benzotriazole group was not enhanced by simply being converted to an *N*-oxides. 2-Alkylbenzotriazoles **1.10**, however, surprisingly reacted with dimethyldioxirane on the aromatic ring to form the corresponding diepoxides **1.11**. This is a rare example of a reaction occurring on the benzene ring of the benzotriazole group.

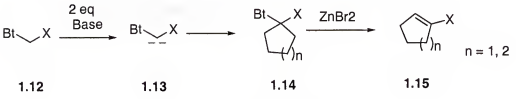


1.8 **1.9**

1.10 **1.11**

Scheme 1-6

Benzotriazolyl group can stabilize an α anion as mentioned above. However, benzotriazole stabilized geminal dianions have not been reported. Geminal dianions (α,α-dianions) have been used primarily to utilize their reactivity and chemoselectivity [1991T4223]. In Chapter 6, we studied the generation of benzotriazole stabilized geminal dianions **1.13**, and their reactions with dihaloalkanes to make cyclic compounds. The benzotriazole group in these compounds can be eliminated to give *N*-cycloalkenyl-azoles **1.15** (Scheme 1-7), a compound class previously rarely reported.



Scheme 1-7

This introduction provided a short overview of benzotriazole methodology as it relates to the synthesis and utility of *N*-substituted benzotriazoles. The following chapters elaborate on the versatility of the benzotriazole group as an excellent synthetic auxiliary in details.

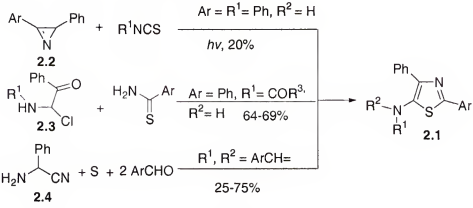
CHAPTER 2
CONVENIENT SYNTHESIS OF 5-ARYLAMINO-2,4-DIARYLTHIAZOLES

2.1 Introduction

Many thiazoles have been reported as important pharmaceuticals [1998CPB632], [1999CB305], [1998JAF263], [1972MI1] dyes, and photographic chemicals [1979MI154]. Simple 2,4-diarylthiazoles, readily synthesized by Hantzsch reactions [1887CB3118], include 2,4-bis(3-indolyl)thiazoles, which are potent cytotoxic reagents [1999BML569]. Less is known about efficient synthesis of 2,4-diarylthiazoles functionalized at the 5 position. Literature syntheses of 5-arylamino-2,4-diarylthiazoles (**2.1**) include the following (Scheme 2-1): (i) the photoconversion of unstable azirene **2.2** into **2.1** in 20% yield [1972HCA916]; (ii) the condensation of unstable ω-chloro-ω-acylamidoacetophenones (**2.3**) with benzothioamide to give **2.1** in 64-94% yields [1974CH810], which is limited by the need to access of **2.3** via condensation of phenylglyoxal with acid amides and thionyl chloride; (iii) synthesizing 5-arylidenamino-2-aryl-4-phenylthiazoles in 25-75% yields from aminophenylacetonitrile, sulfur and aromatic aldehydes [1974JPR299]. In these syntheses, phenyl was the only 4-substituent and yields were low for the thiazoles bearing electron-withdrawing groups in the 2 position (25%).

To the best of our knowledge, the existing synthetic routes for 5-aminothiazoles [1978T611], [1984JCS430], [1985CL1115], [1988H2177, [1991JOC4645, [1994HC877] have not been used for the synthesis of 2,4-diaryl-5-aminothiozoles. In our group, readily available [1991S703] *N*-arylmethylene[(benzotrazol-1-yl)arylmethyl]amines were used in

1,3-dipolar cycloadditions with alkenes or alkynes for the synthesis of pyrroles and dihydropyrroles [1991S863]. Here, we report the convenient synthesis of 5-arylamino-2,4-diarylthiazoles from such 1,3-dipolar synthons.

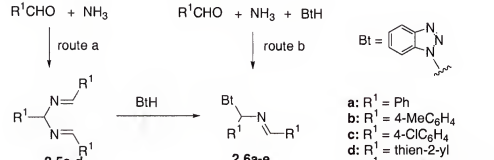


Scheme 2–1

2.2 Results and Discussion

N-Arylmethylene[(benzotrazol-1-yl)arylmethyl]amines **2.6a-c**,**e** (Scheme 2-2) were previously reported to be obtained in high yields by stirring a mixture of benzotriazole, the appropriate arylaldehyde, and methanolic ammonia at rt (Route b) [1991S703]. Compound **2.6e** was reported to be obtained in 90% yield using Route b [1991S703]. However, in the present study, application of the published procedure gave products **2.6a-d** mixed with varying amounts of trimers **2.5a-d**. In a general two-step synthesis (Route a), intermediate trimers **2.5a-d** were readily obtained in 75-90% yields by stirring the corresponding aldehydes and excess (10 fold) aqueous NH_3 (or methanolic ammonia solution) at 20 °C for about 10 h [1837LA130], [1964JOC1985], [1972CJC669]. Subsequent refluxing of **2.5a-d** with benzotriazole in toluene or 1,4-dioxane then gave **2.6a-d** in 80-92% yields. This procedure was particularly suitable for **2.6c** with an electron-withdrawing group, which was obtained in 90% yield. A novel

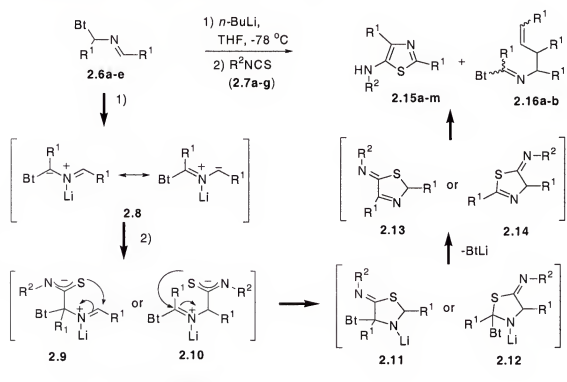
compound **2.6d** functionalized with a thiophene moiety was prepared in 80% yield. Purification on silica gel is not suitable for compounds **2.6a-e** because of the acid-sensitive imine functionality. However, if the imine is solid, recrystallization or removal of excess benzotriazole by washing with saturated Na_2CO_3 solution after reactions provided the pure imines **2.6a-e**.



Scheme 2-2

Treatment of **2.6a-e** with 1 equiv of *n*-BuLi in dry THF at –78 °C resulted in a dark solution immediately, characteristic of carbanions stabilized by a benzotriazole group [1995JOC7612], [1998JOC2110]. Presumably the resonance-stabilized lithiated azomethine ylide **2.8** (Scheme 2-3) was formed. After 5 to 10 min, the appropriate isothiocyanate (R^2NCS, 1.1 equiv) was added dropwise while stirring at –78 °C. The color of the solution changed to dark red about 5 min after the complete addition of the electrophile. Any lack of regioselectivity in providing a mixture of intermediates **2.9** and **2.10** is immaterial since isomers **2.9** and **2.10** both cyclize and then aromatize to the same thiazole **2.15**. Consistent with the hypothesis of azomethine ylide **2.8**, is the observation of a precipitate only 15 minutes after the addition of isothiocyanate at –78 °C. The precipitate was identified by the ^1H NMR spectra to be a complex of the benzotriazole lithium salt with THF. The reaction was monitored by TLC and found to produce mainly

thiazoles **2.15a-m** (Scheme 2-3). That only thiazole and no imidazoles were isolated as final products reflects the nucleophilicity of sulfur.



Scheme 2-3

Thiazoles **2.15a-g** (Table 2-1) were obtained in 35-81% isolated yields as stable solids (except **2.15g** which was oil) from imine **2.6a** and isothiocyanates **2.7a-g**. High yield was obtained for **2.15a** from the reaction of **2.6a** with the simplest substrate **2.7a**. The reaction of **2.6a** with other electron-deficient isothiocyanates **2.7b-d** gave the corresponding products in 56-65% isolated yields. Compared to **2.15d**, a rather low yield of 35% was obtained for **2.15e** from **2.6a** and 2-chlorophenyl isothiocyanate (**2.7e**), possibly due to the steric hindrance of the *ortho*-chloro substituent. For the electron-rich isothiocyanates (**2.7f,g** where R^2 = *p*-MeO, *p*-Me), the precipitate took longer to form in the reaction than for that of the electron-deficient isothiocyanates, and yields were

reasonable (44%, and 55% respectively). The proton NMR spectra of **2.15a-g** all show signals from phenyl rings directly attached to the thiazole ring appearing between 7.2 and 8.0 ppm. Proton signals from the *N*-phenyl rings occur between 6.7 and 7.3 ppm. The NH-proton signals typically show around 5.5 ppm (for **2.15a-d,f,g**), except that for **2.15e** which is shifted downfield to 6.1 ppm.

Table 2-1. Synthesis of thiazole derivatives **2.15a-m**

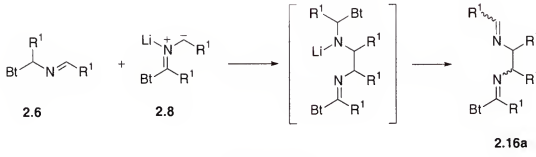
SM	R^1	R^2	Products	Yields (%)**
2.6a, 2.7a	Ph	Ph	**2.15a***	81
2.6a, 2.7b	Ph	3-FC_6H_4	**2.15b**	65
2.6a, 2.7c	Ph	4-FC_6H_4	**2.15c**	60
2.6a, 2.7d	Ph	4-ClC_6H_4	**2.15d**	56
2.6a, 2.7e	Ph	2-ClC_6H_4	**2.15e**	35
2.6a, 2.7f	Ph	4-MeC_6H_4	**2.15f***	44
2.6a, 2.7g	Ph	4-$MeOC_6H_4$	**2.15g**	55
2.6b, 2.7a	4-MeC_6H_4	Ph	**2.15h***	60
2.6c, 2.7a	4-ClC_6H_4	Ph	**2.15i**	61
2.6c, 2.7d	4-ClC_6H_4	4-ClC_6H_4	**2.15j**	80
2.6e, 2.7a	2,4-$(MeO)_2C_6H_3$	Ph	**2.15k**	55
2.6e, 2.7d	2,4-$(MeO)_2C_6H_3$	4-ClC_6H_4	**2.15l**	70
2.6d, 2.7a	Thien-2-yl	Ph	**2.15m**	47

*Compounds were made by Dr. XiaoJing Wang.
**Isolated yields

In the case of **2.6c**, when there was an electron-withdrawing group such as chlorine atom, reactions with isothiocyanates (**2.7a,d**) gave only the desired products (**2.15i,j**) (Table 2-1). The self-condensation product was not detected in the crude reaction mixture. The fact that the self-condensation products were hardly observed from the ^{1}H NMR spectra of crude mixtures is consistent with the relatively stable carbonion **2.8**. The ^{1}H signal of the proton on nitrogen appeared at 5.5 ppm for **2.15i** and 5.6 ppm for **2.15j**.

By-product **2.16** was formed via self-condensation of **2.6** as described in Scheme 2-4. This mechanistic proposal is supported by the fact that **2.16a** (R^1 = Ph) could be

obtained in 50% yield as a single isomer (which isomerized during column chromatography on silica gel) by reacting **2.6a** (2 equiv) with *n*-BuLi (1 equiv).



Scheme 2-4

Products with strong electron-donating groups, like methoxy in **2.15k** and **2.15l**, were obtained in 55% and 70% yields respectively. There are significant shifts in the ^{1}H NMR spectra for the protons of the phenyl ring directly attached to the thiazole ring compared with that of **2.15a-j**. The protons on these phenyl rings show signals in the range between 6.9 and 8.3 ppm. The peak for the proton attached to the nitrogen shifts downfield to between 6.4 and 6.5 ppm. In the ^{1}H NMR spectra of crude mixtures, there were no peaks between 4.00 and 6.00 ppm for the suggested self-condensation products. Possibly, these peaks were also shifted downfield because of the strong electron-donating moieties in the molecule.

1*H*-1,2,3-Benzotriazol-1-yl(2-thienyl)-*N*-[(*E*)-2-thienylmethylidene]methanamine (**2.6d**) was successfully deprotonated and further reacted with phenyl isothiocyanate **2.7a** to result in the final product **2.15m** in reasonable yield. During workup, brine solution was used instead, as 2M NaOH solution decomposed **2.15m** significantly. A minor self-condensation observed from the ^{1}H NMR spectrum of the crude product was represented by two doublet-doublet peaks at 5.28 and 5.53 ppm.

To conclude, we developed a practical and convenient synthesis of 5-arylamino-2,4-diarylthiazoles in moderate-to-good yields. Compared to literature procedures, this method has the advantage of easily available starting materials and simple reaction procedures.

2.3 Experimental Section

Melting points were determined on a MEL-TEMP® capillary melting point apparatus equipped with a Fluke 51 digital thermometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, in $CDCl_3$ referenced to Me_4Si for the ^{1}H spectra and $CDCl_3$ for the ^{13}C spectra. Tetrahydrofuran was distilled under nitrogen from sodium/benzophenone immediately before use. All reactions with moisture-sensitive compounds were carried out under an argon atmosphere. Column chromatography was conducted with silica gel 230-400 mesh.

General procedure for the synthesis of compounds 2.5a–d. Aldehydes (0.1 mol) were added to aqueous NH_3 (1 mol, 30%) or methanolic NH_3 (38 mL, for **2.5d**) solution and the resulting mixture was stirred vigorously for 10 h (or until precipitates formed) at room temperature. The crude products were filtered, washed with water and purified by recrystallizing from ethanol.

Phenyl-*N,N-bis*[(*E*)-phenylmethylidene]methanediamine (2.5a). White solid (95%); mp: 99.0–99.9 °C (Lit.[1906MC839] mp: 103 °C).

(4-Methylphenyl)-*N,N-bis*[(*E*)-(4-methylphenyl)methylidene]methanediamine (2.5b). White solid (80%); mp: 89.3–90.5 °C (Lit.[906MC839] mp: 91 °C).

(4-Chlorophenyl)-*N,N-bis*[(*E*)-(4-Chlorophenyl)methylidene]methane-diamine(2.5c). White microcrystals (85%); mp: 87.8–88.7 °C (Lit.[1964JOC1985] mp: 87–90 °C).

2-Thienyl-*N,N-bis*[(*E*)-2-thienylmethylidene]methanediamine (2.5d). Pale brown microcrystals (75%); mp: 111.0–111.8 °C (Lit.[1911CZ1852] mp: 111.5 °C).

General procedure for the synthesis of compounds 2.6a-d. Compounds **2.5a-d** (20 mmol) and benzotriazole (37 mmol, 1.5 equiv) were dissolved in 1,4-dioxane (for **2.5a**) or toluene (for **2.5b-d**) (100 mL), and the solution was refluxed for 12 h. The reaction mixture was cooled to room temperature, and the solvent was removed. The crude mixture was recrystallized from ethyl acetate/hexane to give **2.6a,d**. Otherwise, the crude mixture was dissolved in ether and washed with saturated aqueous Na_2CO_3 solution to remove excess BtH. The organic layer was dried over $MgSO_4$. The removal of solvent gave **2.6b,c** as yellow oils.

1*H*-1,2,3-Benzotriazol-1-yl(phenyl)-*N*-[(*E*)-phenylmethylidiene]methanamine (2.6a). White powder (92%); mp 115.9–118.4 °C (Lit.[1991S703] mp: 129–130 °C); ^{1}H NMR δ7.31–7.52 (m, 11H), 7.58 (s, 1H), 7.85 (dd, J = 1.8, 8.1 Hz, 2H), 8.05–8.08 (m, 1H), 8.38 (s, 1H); ^{13}C NMR δ83.8, 112.1, 119.8, 124.0, 126.9, 127.3, 128.7, 128.8, 128.9, 129.0, 131.8, 132.0, 134.8, 137.6, 146.7, 164.0.

1*H*-1,2,3-Benzotriazol-1-yl(4-methylphenyl)-*N*-[(*E*)-(4-methylphenyl)-methylidene]-methanamine (2.6b). Yellow oil (93%); ^{1}H NMR δ2.32 (s, 3H), 2.38 (s, 3H), 5.27 (s, 1H), 7.14–7.24 (m, 4H), 7.29–7.37 (m, 4H), 7.46–7.51(m, 2H), 7.72 (d, J = 7.8 Hz, 2H), 8.05–8.28 (m, 1H), 8.32 (s, 1H); ^{13}C NMR δ21.1, 21.6, 83.8, 112.2, 119.8, 123.9, 126.8, 127.2, 128.9, 129.4, 129.5, 131.9, 132.4, 134.9, 138.7, 142.4, 146.8, 163.7.

1*H*-1,2,3-Benzotriazol-1-yl(4-chlorophenyl)-*N*-[(*E*)-(4-chlorophenyl)-methylidene]methanamine (2.6c). Yellow oil (85%); ^{1}H NMR δ7.25–7.43 (m, 9H), 7.53 (s, 1H), 7.76 (d, J = 7.8 Hz, 2H), 8.04–8.08 (m, 1H), 8.29 (s, 1H); ^{13}C NMR δ82.7, 111.6, 119.9, 124.2, 127.6, 128.2, 129.0, 129.1, 130.1, 131.6, 133.0, 134.9, 135.8, 138.2, 146.7, 163.0.

1*H*-1,2,3-Benzotriazol-1-yl(2-thienyl)-*N*-[(*E*)-2-thienylmethylidene]-methanamine (2.6d). Brown powder (80%); mp: 101–102 °C. ^{1}H NMR δ6.90–7.10 (m, 1H), 7.05–7.10 (m, 2H), 7.30–7.39 (m, 4H), 7.50–7.52 (m, 2H), 7.75 (s, 1H), 8.04–8.07 (m, 1H), 8.37 (s, 1H); ^{13}C NMR δ79.6, 112.1, 119.8, 124.1, 126.2, 126.6, 127.2, 127.5, 127.8, 131.3, 131.5, 133.3, 140.7, 140.8, 146.7, 156.9. Anal. Calcd for $C_{16}H_{12}N_4S_2$: C, 59.24; H, 3.73; N, 17.27. Found: C, 59.26; H, 3.72; N, 17.17.

Procedure for the synthesis of 1*H*-1,2,3-benzotriazol-1-yl(2,4-dimethoxyphenyl)-*N*-[(*E*)-(2,4-dimethoxyphenyl)methylidene]methanamine (2.6e). 2,4-Dimethoxybenzaldehyde (5 g, 30 mmol) was dissolved in 18 mL of absolute ethanol, followed by the addition of benzotriazole (7.6 g, 75 mmol) and methanolic ammonia (17 mL, 75 mmol) and stirred overnight at rt. White precipitate was filtered and washed with cold ethanol to give **2.6e** as a white powder in 90% yield; mp: 161.6–163.2 °C (Lit.[1991S703] mp: 166–167 °C). ^{1}H NMR δ3.63 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 6.40 (d, J = 5.4 Hz, 2H), 6.52 (t, J = 9.9 Hz, 2H), 7.26–7.32 (m, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.64 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 8.00–8.08 (m, 2H), 8.76 (s, 1H); ^{13}C NMR δ55.3, 55.4, 79.2, 97.8, 98.5, 104.1, 105.6, 111.7, 117.0, 118.9, 119.6, 123.4, 126.7, 129.1, 129.4, 132.4, 146.3, 158.1, 158.7, 160.8, 161.4, 163.9.

General procedure for the synthesis of compounds 2.15a–m. *n*-BuLi (1.6 M in hexane, 4 mmol) was added to a solution of the corresponding *N*-arylmethylene-[benzotriazol-1-yl)arylmethyl]amines **2.6** (4 mmol) in THF (50 mL) at –78 °C under argon. After stirring for 5 min, isothiocyanate (4.4 mmol) was added. The reaction mixture was allowed to warm-up to rt, quenched with 2 M NaOH or brine solution (30 mL). After the separation, the aqueous layer was extracted with Et_2O (2x20 mL). The combined organic layer was dried (Na_2SO_4), and the solvent was removed. The product was purified by flash chromatography using pentane and diethyl ether as the eluent.

***N*-2,4-Triphenyl-1,3-thiazol-5-amine (2.15a):** Yellow microcrystals (81%); mp 125.0–125.7 °C. (Lit.[1972HCA916] mp: 122.5–124.0 °C); ^{1}H NMR δ 5.48 (br s, 1H), 6.84–6.91 (m, 3H), 7.19–7.39 (m, 8H), 7.92–7.94 (m, 4H); ^{13}C NMR δ 114.8, 120.4, 126.1, 127.7, 127.8, 128.6, 128.8, 129.5, 129.7, 133.9, 134.0, 135.6, 145.3, 146.7, 160.6. Anal. Calcd for $C_{21}H_{16}N_2S$: C, 76.80; H, 4.91; N, 8.53. Found: C, 77.09; H, 5.03; N, 8.61.

***N*-(3-Flourophenyl)-2,4-diphenyl-1,3-thiazol-5-amine (2.15b).** Yellow microcrystals (65%); mp: 119.7–120.2 °C; ^{1}H NMR δ 5.57 (s, H), 6.56–6.65 (m, 3H), 7.17–7.32 (m, 1H), 7.34–7.46 (m, 6H), 7.91–7.97 (m, 4H); ^{13}C NMR δ 101.7 (d, J = 25.6 Hz), 106.9 (d, J = 21.0 Hz), 110.2 (d, J = 2.5 Hz), 127.8, 128.1, 128.6, 128.9, 130.0, 130.7 (d, J = 10.1 Hz), 133.7, 133.8, 134.1, 147.3 (d, J = 10.1 Hz), 147.9, 161.9, 162.9 (d, J = 243.3 Hz). Anal. Calcd for $C_{21}H_{15}FN_2S$: C, 72.81; H, 4.36; N, 8.09. Found: C, 72.46, H, 4.33; N, 8.03.

***N*-(4-Flourophenyl)-2,4-diphenyl-1,3-thiazol-5-amine (2.15c).** Yellow microcrystals (61%); mp: 109.5–110.5 °C; ^{1}H NMR δ 5.50 (s, 1H), 6.84–6.88 (m, 2H), 6.94–7.00 (m, 2H), 7.31–7.38 (m, 1H), 7.41–7.44 (m, 5H), 7.93–7.96 (m, 4H); ^{13}C NMR

δ 116.1, 116.2 (d, J = 22.2), 126.1, 127.7, 127.9, 128.7, 128.9, 129.8, 133.9, 134.0, 136.1, 141.6, 146.5, 155.9, 159.8 (d, J = 102.5). Anal. Calcd for $C_{21}H_{15}FN_2S$: C, 72.81; H, 4.36; N, 8.09. Found: C, 72.87; H, 4.53; N, 8.03.

***N*-(4-Chlorophenyl)-2,4-diphenyl-1,3-thiazol-5-amine (2.15d).** Yellow microcrystals (56%); mp: 128.0–129.3 °C; ^{1}H NMR δ 5.5 (s, 1H), 6.78 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 7.23–7.42 (m, 6H), 7.90–7.95 (m, 4H); ^{13}C NMR δ 115.8, 125.2, 126.2, 127.8, 128.0, 128.6, 128.9, 129.4, 130.0, 133.8, 134.8, 144.0, 147.5, 161.4. Anal. Calcd for $C_{21}H_{15}ClN_2S$: C, 69.51; H, 4.17; N, 7.72. Found: C, 69.32, H, 4.22; N, 7.69.

***N*-(2-Chlorophenyl)-2,4-diphenyl-1,3-thiazol-5-amine (2.15e).** Yellow microcrystals (35%); mp: 108.1–109.5 °C; ^{1}H NMR δ 6.11 (s, 1H), 6.81 (dt, J = 8.1, 1.5 Hz, 1H), 6.96 (dd, J = 8.4, 1.5 Hz, 1H), 7.13 (td, J = 8.4, 1.2 Hz, 1H), 7.31–7.46 (m, 7H), 7.95–7.99 (m, 4H); ^{13}C NMR δ 114.2, 120.0, 120.5, 126.3, 127.7, 128.0, 128.1, 128.6, 128.9, 129.4, 130.0, 133.5, 133.7, 133.9, 141.7, 148.5, 162.2. Anal. Calcd for $C_{21}H_{15}ClN_2S$: C, 69.51; H, 4.17; N, 7.72. Found: C, 69.63; H, 4.23; N, 7.66.

***N*-(4-Methylphenyl)-2,4-diphenyl-1,3-thiazol-5-amine (2.15f).** Yellow microcrystals (44%); mp: 101.1–103.0 °C; ^{1}H NMR δ 2.29 (s, 3H), 5.51(s, H), 6.85 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 7.30–7.38 (m, 1H), 7.38 –7.42 (m, 5H), 7.92–7.96 (m, 4H); ^{1}C NMR δ 20.6, 115.2, 126.1, 127.6, 127.7, 128.6, 128.8, 129.7, 130.0, 130.2, 134.0, 134.2, 136.6, 142.8, 145.7, 159.8. Anal. Calcd for $C_{22}H_{18}N_2S$: C, 77.16; H, 5.30; N, 8.18. Found: C, 76.83; H, 5.47; N, 8.13.

***N*-(4-Methoxylphenyl)-2,4-diphenyl-1,3-thiazol-5-amine (2.15g).** Pale yellow oil (55%); ^{1}H NMR δ 3.71 (s, 3H), 5.47 (s, H), 6.81 (q, J = 9.0, 15.3 Hz, 4H), 7.23–7.38

(m, 6H), 7.88–7.94 (m, 4H); ^{13}C NMR δ55.5, 114.8, 117.0, 125.9, 127.5, 127.6, 128.5, 128.7, 129.5, 134.0, 134.2, 138.1, 138.8, 144.5, 154.3, 158.8. Anal. Calcd for $C_{22}H_{18}N_2OS$: C, 73.71; H, 5.06; N, 7.81. Found: C, 73.26; H, 5.51; N, 7.79.

***N*-[2,4-*bis*(4-Methylphenyl)-1,3-thiazol-5-yl]-*N*-phenylamine (2.15h).** Yellow needles (60%); mp: 143.2–143.3 °C; ^{1}H NMR δ2.34 (s, 3H), 2.37 (s, 3H), 5.45 (s, 1H), 6.86–6.90 (m, 3H), 7.17–7.27 (m, 6H), 7.81–7.85 (m, 4H); ^{13}C NMR δ21.3, 21.4, 114.6, 120.2, 126.0, 127.7, 129.2, 129.5, 131.3, 131.4, 134.4, 137.6, 139.9, 145.5, 147.0, 161.1. Anal. Calcd for $C_{23}H_{20}N_2S$: C, 77.49; H, 5.65; N, 7.86. Found: C, 77.43; H, 5.71; N, 7.84.

2,4-*bis*(4-Chlorophenyl)-*N*-phenyl-1,3-thiazol-5-amine (2.15i). Yellow crystal (61%); mp: 44.5–45.5 °C; ^{1}H NMR δ5.50 (s, 1H), 6.86–6.96 (m, 3H), 7.24–7.29 (m, 2H), 7.32–7.41 (m, 4H), 7.83–7.93 (m, 4H); ^{13}C NMR δ114.9, 120.9, 127.3, 128.8, 129.0, 129.1, 129.6, 132.3, 133.7, 135.9, 136.3, 144.9, 145.8, 159.6. Anal. Calcd for $C_{21}H_{14}Cl_2N_2S$: C, 63.48; H, 3.55; N, 7.05. Found: C, 63.31; H, 3.65; N, 6.84.

***N*,2,4-*tris*(4-Chlorophenyl)-1,3-thiazol-5-amine (2.15j).** Yellow microcrystals (80%); mp: 73.4–74.6°C; ^{1}H NMR δ5.54 (s, 1H), 6.73 (d, J = 9.0 Hz, 2H), 7.16–7.19 (m, 2H), 7.23–7.38 (m, 4H), 7.82 (t, J = 7.8 Hz, 4H); ^{13}C NMR δ115.8, 125.5, 127.2, 128.7, 128.9, 129.1, 129.4, 131.9, 132.0, 133.7, 135.4, 136.0, 143.6, 146.3, 160.2. Anal. Calcd for $C_{21}H_{13}Cl_3N_2S$: C, 58.42; H, 3.03; N, 6.49. Found: C, 58.60; H, 3.15; N, 6.51.

2,4-*bis*(2,4-Dimethoxyphenyl)-*N*-phenyl-1,3-thiazol-5-amine (2.15k). Yellow microcrystals (55%); mp: 141.7–144.3 °C; ^{1}H NMR δ3.81 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 3.92 (s, 3H), 6.48–6.64 (m, 5H), 6.80 (t, J = 7.2 Hz, 1H), 6.98 (d, J = 8.4 Hz, 2H), 7.19 (t, J = 7.5 Hz, 2H,), 7.63 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 9.0 Hz, 1H); ^{13}C NMR δ 55.3, 55.4, 55.5, 56.1, 98.2, 99.3, 105.5, 105.9, 114.7, 116.3, 117.1, 119.6, 128.8, 129.1,

132.3, 136.6, 139.2, 145.2, 152.4, 156.9, 157.0, 160.7, 161.3. Anal. Calcd for $C_{25}H_{24}N_2O_4S$: C, 66.94; H, 5.39; N, 6.25. Found: C, 66.56; H, 5.21; N, 6.16.

2,4-*bis*(2,4-Dimethoxyphenyl)-*N*-(4-chloro)phenyl-1,3-thiazol-5-amine (2.15l). Yellow microcrystals (70%); mp: 151.5–153 °C; ^{1}H NMR δ 3.83 (s, 6H), 3.84 (s, 3H), 3.85 (s, 3H), 6.43 (s, 1H), 6.52–6.65 (m, 4H), 6.88 (d, J = 9.0 Hz, 2H), 7.13 (d, J = 9.0 Hz, 2H), 7.62 (d, J = 8.4 Hz, 1H$_x$), 8.32 (d, J = 8.7 Hz, 1H$_x$); ^{13}C NMR δ 55.4, 55.5, 55.6, 56.3, 98.3, 99.4, 105.6, 105.9, 115.9, 116.2, 117.0, 124.1, 128.9, 129.0, 132.3, 135.9, 139.9, 144.0, 153.1, 156.9, 157.1, 160.8, 161.5. Anal. Calcd for $C_{25}H_{23}ClN_2O_4S$: C, 62.17; H, 4.80; N, 5.80. Found: C, 62.39; H, 5.02; N, 5.81.

***N*-Phenyl-2,4-di(2-thienyl)-1,3-thiazol-5-amine (2.15m):** Yellow microcrystals (47%); mp: 141.1–143.1 °C; ^{1}H NMR δ 5.39 (s, 1H), 6.83–6.88 (m, 2H), 6.91 (d, J = 7.5 Hz, 1H), 7.01–7.06 (m, 2H), 7.22–7.27 (m, 3H), 7.37–7.42 (m, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.60 (d, J = 3.6 Hz, 1H); ^{13}C NMR δ 114.7, 120.6, 125.7, 125.8, 126.4, 127.3, 127.8, 129.5, 132.3, 136.1, 137.7, 143.0, 144.9, 156.0. Anal. Calcd for $C_{17}H_{12}N_2S_3$: C, 59.97; H, 3.55; N, 8.23. Found: C, 59.94; H, 3.64; N, 8.12.

The preparation of *N*-[1*H*-1,2,3-benzotriazol-1-yl(phenyl)methylidene]-*N*-[phenylmethylidene]-1,2-(1,2-diphenyl)ethanediamine (2.16a). The amine **2.6a** (1.24 g, 4 mmol) was dissolved in dry THF (40 mL) under argon, *n*-BuLi was added (1.4 mL, 2 mmol) at –78 °C. The reaction mixture was allowed to warm up to rt. gradually and was quenched with saturated NH_4Cl solution (30 mL). The organic layer was separated and the aqueous layer was extracted using Et_2O (20 mL × 2). The combined organic layers were dried over Na_2SO_4. After the removal of the solvent, the crude mixture was purified by column chromatography on silica-gel using Et_2O: pentane (1:1) to give a mixture of

isomers as a yellow powder (0.5 g, 50%). mp: 216.0–224.7 °C; ^{1}H NMR δ 5.07 (d, J = 6.6 Hz, 1H), [5.10 (d, J = 6.0 Hz, 1H)], 5.17 (d, J = 6.6 Hz, 1H), [5.43 (d, J = 6.0 Hz, 1H)], 6.43 (d, J = 8.1 Hz, 1H), 6.81–7.77 (m, 23H), [6.81–7.77 (m, 25H)], 7.99 (d, J = 8.4 Hz, 1H). Anal. Calcd for $C_{34}H_{27}N_5$: C, 80.77; H, 5.38; N, 13.85. Found: C, 80.62; H, 5.46; N, 13.65.

CHAPTER 3

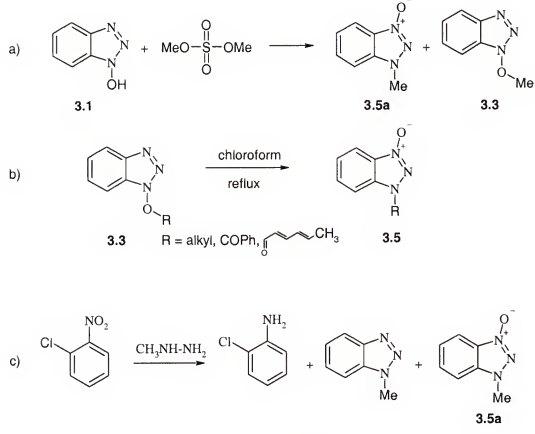
CONVERSIONS BY DIMETHYLDIOXIRANE OF 1-ALKYLBENZOTRIAZOLES INTO THEIR *N*-OXIDES AND OF 2-ALKYLBENZOTRIAZOLES INTO 2-ALKYL-*TRANS*-4,5,6,7-DIEPOXY-4,5,6,7-TETRAHYDROBENZOTRIAZOLES

3.1 Introduction

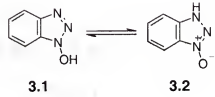
Although *O*-acyl derivatives of 1-hydroxybenzotriazole are of considerable synthetic use [1970CB788], [1977JCR(S)182], [1972MI343] there has been little investigation of the *N*-oxides of *N*-alkylbenzotriazoles. The present work was planned to develop a reliable synthetic pathway to the *N*-alkylbenzotriazole *N*-oxides and to study the properties of the oxidized benzotriazolyl group as a nucleofuge. Previously, three synthetic approaches to 3-substituted benzotriazole 1-oxides **3.5** have been reported (Scheme 3-1). (a) The *N*-alkylation of 1-hydroxybenzotriazole (**3.1**) (which gave mixtures of **3.5a** with 1-alkoxybenzotriazoles **3.3**) was chronologically the first [1923JCS2258], [1928JCS198] and has been further investigated [1950JCS767]. (b) Closely related is the isomerization of 1-alkoxybenzotriazoles (**3.3**) into **3.5** in refluxing chloroform, [1980FES240] and the rearrangement of 1-benzoyloxybenzotriazoles into 3-benzoylbenzotriazole 1-oxide [1991JSC(P2)1545] and 1-(α,β-unsaturated acyloxy)-benzotriazoles into the corresponding 3-acylbenzotriazole 1-oxides [1985JO2174]. (c) The reaction of 2-chloronitrobenzene with methylhydrazine gave 3-methylbenzotriazole 1-oxide **3.5a** along with various other products [1999H693].

1-Hydroxybenzotriazole (**3.1**) and 3*H*-benzotriazole 1-oxide (**3.2**) (Scheme 3-2) exist in a tautomeric equilibrium, which has been much studied by physical methods

[1972JCS(P2)160], [1995SA(A)1801]. The position of the equilibrium depends on the solvents used: in more polar solvent water the *N*-oxide form dominates, whereas in less-polar solvent ethanol, approximately 80% of the *N*-hydroxy form is present at equilibrium [1974BSF3049] [1980OMR339]. The NMR [1980OMR339] and mass spectra [1974BSF3049] of benzotriazole 1-oxides have been reported.



Scheme 3-1



Scheme 3-2

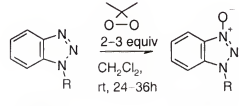
To the best of our knowledge, no direct *N*-oxidations of 1-alkylbenzotriazoles have been previously recorded, although 1-substituted 1,2,3-triazoles were oxidized to the corresponding *N*-oxides using *m*-chloroperbenzoic acid [1987ACS724]. 2-Methylbenzotriazole 1-oxide was obtained by oxidation of 2-methylbenzotriazole, but in only 0.2% yield [1972JCS(P2)160]. In the present work, we studied the direct oxidation of 1- and 2-alkylbenzotriazoles by dimethyldioxirane (DMD), known to be an effective oxidizing agent for the *N*-oxidation of pyridines [1985JOC2847] [1997T15877], imines [1990JCS(P1)301], and tertiary amines [1997T15877].

3.2 Results and Discussion

Our study demonstrated that 1- and 2-alkylbenzotriazoles on treatment with DMD show completely divergent chemical behavior. Reactions of 1-alkylbenzotriazoles **3.4a-l** with DMD led to *N*-oxidation to give the corresponding 3-alkylbenzotriazole 1-oxides **3.5a-l** (Scheme 3-3, Table 3-1). By contrast, 2-alkylbenzotriazoles **3.12a**,**b** underwent oxidation in the aromatic ring to give previously unknown *trans*-4,5,6,7-diepoxy-4,5,6,7-tetrahydrobenzotriazoles **3.13a**,**b** (Scheme 3-8).

Oxidation of 1-alkylbenzotriazoles. We oxidized a number of 1-alkyl benzotriazole derivatives **3.4** with DMD using two alternative methods. In method A, 1-methylbenzotriazole **3.4a** was treated with a 0.08 M solution of DMD in acetone [1991CB2377]. This led to the corresponding 3-methyl 1-oxide **3.5a** in 42% yield after purification by column chromatography on silica gel. The DMD solution was added to the substrate in two or three portions with 18 h intervals. The consumption of **3.4a** was monitored by TLC. Even with a threefold molar excess of oxidizer, a significant amount of unreacted **3.4a** remained in the crude reaction mixture containing **3.5a**. In method B,

one equivalent of a 0.2-0.3 M solution of DMD in CH_2Cl_2 [1997T8643] was used; after 12 to 18 h, the solvent was evaporated and another equivalent of DMD was added. In the cases of **3.4e** to **3.5e** and **3.4f** to **3.5f**, the evaporation and the addition of DMD was repeated for a third time to complete the reaction. Method B, while providing good to excellent yields of products, required an additional step for the preparation of the concentrated DMD solution. The yields obtained by method B are summarized in the Table 3-1. The reaction tolerates various alkyl, functionalized alkyl and arylalkyl substituents. However, electron withdrawing groups in the starting benzotriazoles **3.4i**, **3.4k**, **3.4l** reduce the yields (Table 3-1). Electron deficient 1-benzoylbenzotriazole **3.4m** was inert to DMD.



3.4a-l **3.5a-l**

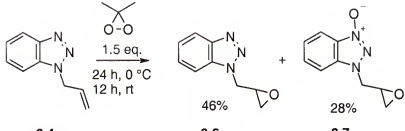
Scheme 3-3 (See Table 3-1 for R)

The oxidation of 1-substituted benzotriazoles by DMD is complicated by the presence of a C=C double bond in the structure. Whereas DMD rapidly oxidizes pyridines and tertiary amines selectively at 0 °C into their *N*-oxides in the presence of C=C bonds [1997T15877], 1-allylbenzotriazole (**3.4n**) is slowly oxidized preferentially at the C=C bond at 0 °C for 24 h. Complete conversion of 1-allylbenzotriazole occurred only at 20 °C and gave a mixture of, 1-(2-oxiranylmethyl)-1*H*-benzotriazole **3.6** (46%) and 3-(2-oxiranylmethyl)-3*H*-benzotriazole 1-oxide **3.7** (28%) (Scheme 3-4). Evidently the first formed epoxide **3.6** underwent further oxidation to **3.7**. As expected 1-alkyl-

benzotriazoles are less reactive toward DMD compared to pyridines and tertiary amines [1997T15877] which are easily oxidized at 0 °C.

Table 3-1. Synthesis of *N*-oxides **3.5** *via* oxidation of 1-alkylbenzotriazoles by DMD (method B)

Compound	R	DMD (equiv)	Reaction time h	Yield %
3.5a	Me	2.0	24	90
3.5b	Et	2.0	24	74
3.5c	*n*-Pr	2.0	24	76
3.5d	*n*-C_6H_{13}	2.0	34	81
3.5e	*n*-C_9H_{19}	3.0	48	90
3.5f	CH_2Ph	3.0	48	92
3.5g	CH_2CH_2Ph	2.2	48	92
3.5h	$CHCH_3Ph$	2.0	48	73
3.5i	CH_2CO_2Me	3.0	36	68
3.5j	CH_2OPh	3.0	36	91
3.5k	$CH_2C{\equiv}CH$	3.0	60	35
3.5l	CH_2CN	3.0	60	40
3.5m	COPh	2.0	48	0



Scheme 3-4

Structure of 3-substituted benzotriazole 1-oxides. The ^{13}C NMR spectrum ($CDCl_3$) obtained for 3-methylbenzotriazole 1-oxide **3.5a** matches that described earlier [1980OMR339]. The signal of C-7a eclipsed by C-5 was revealed by APT. The ^1H NMR ($CDCl_3$) of 3-methylbenzotriazole 1-oxide **3.5a** differs significantly from that of **3.4a**: thus, the methyl group resonance (4.10 ppm) of 3-methylbenzotriazole 1-oxide **3.5a**

was 0.20 ppm upfield of that of 1-methylbenzotriazole **3.4a**. The aromatic protons of **3.5a** are well resolved due to the shielding effect of N-O group, four separate groups of peaks appeared at: 7.36–7.44 (m, 1H, H-5), 7.49 (d, J = 8.5 Hz, 1H, H-4), 7.58–7.66 (m, 1H, H-6), 7.82 (d, J = 8.5 Hz, 1H, H-7). This characteristic pattern is repeated in the proton spectra of each of the 3-substituted benzotriazole 1-oxide **3.5**, except for those containing an aromatic ring in the 3-substituent (**3.5f-h**, **3.5j**). For **3.5f-h**, **3.5j**, the doublet for H-7 and the multiplet for H-6 are clearly separated, while the signals for H-4 and H-5 are covered under the phenyl ring multiplets of the 3-substituent.

The structure of 3-methylbenzotriazole 1-oxide **3.5a**, as a hemihydrate, was determined by single crystal X-ray crystallography (Figure 3-1) by Dr. Peter Steel. The water molecule lies on a two-fold crystallographic rotation axis, and connects two molecules of the *N*-oxide by linear intermolecular hydrogen bonds. The molecular geometry of the *N*-oxide molecule is very similar to that of the parent 3*H*-benzotriazole 1-oxide **3.1** [1983AX(C)1089]; In each case, the N3-N2 bond is significantly longer than the N2-N1 bond.

The reactivity of 3-substituted benzotriazole 1-oxides. A strong nucleophile, thiophenol anion did not displace the benzotriazole 1-oxide residue in **3.5f** on refluxing in ethanol or toluene, for up to 36 h; the starting material **3.5f** was recovered. Conversion of the benzotriazole **3.4f** into the corresponding *N*-oxide **3.5f** thus does not increase its nucleofugacity sufficiently to allow easy displacement of an unactivated benzyl group.

Refluxing of **3.5e** in neat acetic anhydride gave deoxygenated 1-nonyl-benzotriazole **3.4e**. No appreciable loss of the nonyl group as nonylaldehyde or conversion of **3.5e** into 1-benzotriazolyl nonylacetate **3.8** occurred (Scheme 3-5). For

comparison, reaction of 2-methylpyridine *N*-oxide with acetic anhydride leads to the corresponding 2-pyridinylmethyl acetate [1974JOC2916].

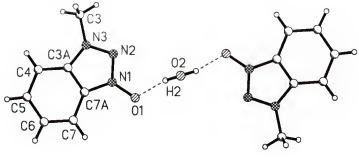
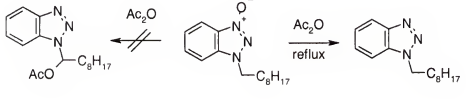


Figure 3-1. X-ray structure of **3.5a,** showing the intermolecular hydrogen bonding. The asymmetric unit is labeled. Selected interatomic distances (Å) and angles (°): O1-N1 1.295(1); N1-N2 1.316(2); N2-N3 1.345(2); N3-C3 1.448(2); H2-O2 0.88(2); H2-O1 1.98(2); O1···O2 2.848(1); O1-N1-N2 121.5(1); N1-N2-N3 105.7(1); N2-N3-C3 119.5(1); O2-H1···O2 169(1).

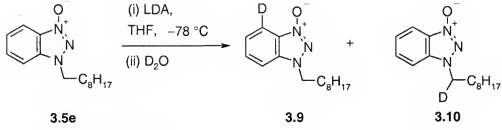


3.8 **3.5e** **3.4e**

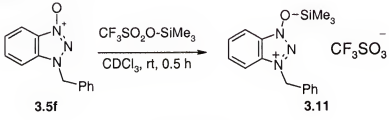
Scheme 3-5

In study of the lithiation of benzotriazole 1-oxides **3.5** with a strong base, 3-nonylbenzotriazole 1-oxide (**3.5e**) was treated with LDA in THF at –78 °C for 15 min and then quenched with D_2O. The ^1H NMR spectrum of products showed that deuterium was incorporated roughly in about 90% on the 7-position of the benzotriazole 1-oxide ring and only partially (about 5%) in the alpha position of the benzotriazole 1-oxide alkyl chain, to give **3.9** and **3.10**, respectively (Scheme 3-6). Incorporation of deuterium in the 4-position was not observed. This shows that the 1-position N-O group greatly increases the acidity of the 7-position CH, possibly by coordination in the transition state. 1-*n*-

Alkylbenzotriazoles are lithiated mainly at the CH_2 group adjacent to N and subsequently reacted with electrophiles [1994LA1]. However, 1-isopropyl benzotriazole undergo lithiation predominantly on the benzenoid ring in the 4-position (about 32%), 7-position (about 8%) and a little (about 2%) at $CH(CH_3)_2$ adjacent to N [1995JOC1244].



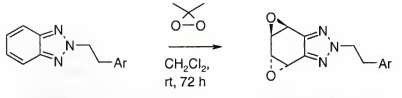
Scheme 3-6



Scheme 3-7

N-Oxide **3.5f** reacted with trimethylsilyl trifluoromethanesulfonate in $CDCl_3$ solution to give *in-situ* 1-(trimethylsilyloxy)-3-benzylbenzotriazolium trifluoromethanesulfonate (**3.11**) (Scheme 3-7). Compound **3.11** was characterized by NMR: the ^1H spectrum shows the resonance of the CH_2 adjacent to N shifted downfield to 5.95 ppm compared to 5.57 ppm of *N*-oxide **3.5f**. The changes of ^{13}C chemical shifts are even more pronounced, in that CH_2 shifted down field to 55.7 ppm compared to 52.7 ppm of the parent *N*-oxide; C-7 and C-4 showed a similar chemical shifts at 113.3 ppm and 113.2 ppm; resonances of C-6 and C-5 appeared at 131 and 130 ppm, the chemical shifts of C-

7a and C-4a were 130.8 and 130.4 ppm. This indicated that the positive charge in the benzotriazolium ring is now evenly distributed between N-1 and N-3.



3.12a,b
a: Ar = C_6H_5; **b**: Ar = *p*-$NO_2C_6H_4$

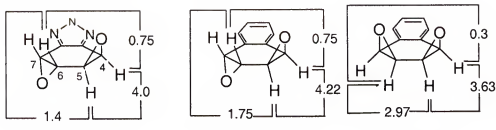
3.13a (50%); **3.13b** (77%)

Scheme 3-8

Oxidation of 2-alkylbenzotriazoles. In contrast to the conversion of 1-alkylbenzotriazole (**3.4a-l**) into 3-alkylbenzotriazole 1-oxides (**3.5a-l**), a twofold excess of DMD in methylene chloride at ambient temperature converted 2-alkylbenzotriazoles **3.12a,b** into the corresponding *trans*-4,5,6,7-diepoxy-4,5,6,7-tetrahydrobenzotriazoles **3.13a,b** (Scheme 3-8). The NMR spectra of the reaction mixtures showed only the diepoxides **3.13a,b** along with unreacted **3.12a,b**, but no products of *N*-oxidation or other side reactions. Compounds **3.13a,b** were isolated using column chromatography on silica gel. They are quite stable and can be stored neat in the air or in $CDCl_3$ solution at ambient temperature without any sign of decomposition for weeks. In contrast, the literature records the instability of *trans*-5,6,7,8-diepoxy-5,6,7,8-tetrahydroquinoline in the air [1991JCS(P1)2189].

The *trans* orientation of the epoxide rings in **3.13a** was assigned unambiguously from the vicinal coupling constants of the position 5 and 6 protons. Coupling constants obtained by analysis of the AA′BB′ system for compound **3.13a** are comparable to those published for *trans*-1,2,3,4-diepoxy-1,2,3,4-tetrahydronaphthalene (**3.14**) [1976AGE229] (Figure 3-2). Although both vicinal coupling constants $J_{4,5}$ and $J_{5,6}$ in **3.13** are slightly

smaller than those of **3.14**, a coupling constant of $J_{5,6}$ = 1.4 Hz is much closer to corresponding coupling constant for *trans* protons in **3.14** (1.75 Hz) than for *cis* protons in *cis*-naphthalene dioxide **3.15** (2.97 Hz) (Figure 2.2) [1976AGE229].



3.13a **3.14** **3.15**

Figure 3-2. Coupling constants obtained from simulation of spectra for compound **3.13a** and those for two isomers of naphthalene dioxide **3.14** and **3.15**.

Arene oxides are of considerable interest due to their relationship to the mutagenic and carcinogenic properties of certain polycyclic aromatic hydrocarbons (PAH) [1982CR4875]. Naphthalene is converted by DMD into *trans*-1,2,3,4-diepoxy-1,2,3,4-tetrahydronaphthalene (**3.14**-*trans*) in only 5% yield [1984JA2462], but the more reactive methyl(trifluoromethyl)dioxirane gave a 90% conversion [1990TL6097]. Compounds of type **3.13,** diepoxybenzenes fused with a triazole ring, previously unreported, are of potential interest for mutagenic/carcinogenic properties [1982CR4875], [1974NAT326].

3.3 Conclusion

We studied the oxidation of alkylbenzotriazoles by dimethyldioxirane in dichloromethane solution. Oxidation of 1-alkylbenzotriazoles **3.4** by DMD is a highly efficient synthetic pathway to the 3-alkylbenzotriazole 1-oxides **3.5**. The reaction is limited for compounds containing oxidizable substituents. Position 7 in 3-

alkylbenzotriazole 1-oxides **3.5** is activated toward proton loss under the action of a strong base. The oxygen atom in 3-alkylbenzotriazole 1-oxides can be silylated to form trimethylsilyloxybenzotriazolium salt or removed by reflux with acetic anhydride. Oxidation of 2-alkylbenzotriazoles **3.12** by DMD led to the 2-alkyl-*trans*-4,5,6,7-diepoxy-4,5,6,7-tetrahydrobenzotriazoles **3.13**, described here for the first time.

3.4 Experimental Section

Melting points were determined on a MET-TEMP® capillary melting point apparatus equipped with a Fluke 51 digital thermometer, and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, in $CDCl_3$ referenced to Me_4Si for the ^{1}H spectra and $CDCl_3$ for the ^{13}C spectra. Tetrahydrofuran was distilled under nitrogen from sodium-benzophenone immediately before use. All reactions with moisture-sensitive compounds were carried out in a dry nitrogen atmosphere. The 1- and 2-alkyl-1*H*-1,2,3-benzotriazoles were prepared accordingly to the previously reported procedures [1935LA113]. Dimethyldioxirane solutions were prepared as described in sources [1991CB2377], [1997T8643], [1997T15877]. X-ray structure of **3.5a** was done by Dr. Peter J. Steel at the Department of Chemistry, University of Canterbury, Christchurch, in New Zealand.

General procedure for the oxidation of alkylbenzotriazoles 3.4 (Method B). Alkylbenzotriazole (1 mmol, 5 mL) was placed in a dry flask, dissolved in 0.2 M solution of DMD (1 mmol) in dichloromethane and stirred at rt. for 18 h. The solvent was removed and another equivalent of the DMD solution was added. The reaction was monitored by TLC. If necessary, a third equivalent of DMD was added (see Table 3-1). After another 12 to18 h, the solvent was removed to give a brown oil, which was purified

either by column chromatography using 25 to 30% acetone in pentane, or by recrystallization from ethyl acetate.

3-Methyl-3*H*-1,2,3-benzotriazole 1-oxide (3.5a). Brown prisms (90%) (from ethyl acetate); mp: 141.5–145.5 °C; ^{1}H NMR δ 4.10 (s, 3H), 7.36–7.44 (m, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.58–7.66 (m, 1H), 7.82 (d, J = 8.5 Hz, 1H); ^{13}C NMR δ 34.6, 110.1, 115.7, 124.2, 130 (2C), 134.4. Anal. Calcd for $(C_7H_7N_3O)_2{\cdot}H_2O$: C, 53.16; H, 5.10; N, 26.57. Found: C, 53.44; H, 5.16; N, 26.66.

Crystal data for 3.5a: $C_7H_7N_3O.0.5H_2O$, FW 158.16, monoclinic, space group C2/c, a = 20.451(7), b = 6.767(2), c = 13.471(4) Å, β = 129.259(3) °, V = 1443(1) Å ^{3}, F(000) = 664, Z = 8, T = -110 °C, μ (MoKα) = 0.11 mm^{-1}, D_{calcd} = 1.456 g.cm^{-3}, $2\theta_{max}$ 53° (CCD area detector, MoKα radiation), GOF = 1.07, wR(F^2) = 0.105 (all 1472 data), R = 0.034 (1212 data with $I > 2\sigma I$).

3-Ethyl-3*H*-1,2,3-benzotriazole 1-oxide (3.5b). Brown prisms (74%) (from ethyl acetate/ hexanes); mp: 61–62 °C; ^{1}H NMR δ 1.60 (t, J = 7.16 Hz, 3H), 4.45 (q, J = 7.15 Hz, 2H), 7.36–7.44 (m, 1H), 7.51 (d, J = 8.7 Hz, 1H), 7.57–7.65 (m, 1H), 7.98 (d, J = 8.7, 1H); ^{13}C NMR δ 14.6, 43.6, 110.1, 115.7, 124.1, 130.1, 130.2, 133.5. Anal. Calcd for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.81; H, 5.75; N, 25.32.

3-Propyl-3*H*-1,2,3-benzotriazole 1-oxide (3.5c). White prisms (76%) (from ethyl acetate /hexanes); mp: 71–73 °C; ^{1}H NMR δ 0.98 (t, J = 7.5 Hz, 3H), 1.95–2.10 (m, 2H), 4.36 (t, J = 7.5 Hz, 2H), 7.34–7.42 (m, 1H), 7.48–7.54 (m, 1H), 7.58–7.64 (m, 1H), 7.99 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 11.4, 23.1, 50.4, 110.4, 116.0, 124.4, 130.4 (2C), 134.3. Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 60.78; H, 6.36; N, 23.71.

3-Hexyl-3*H*-1,2,3-benzotriazole 1-oxide (3.5d). Brown oil (81%); ^{1}H NMR δ 0.87 (t, J = 3.4 Hz, 3H), 1.20–1.40 (m, 6H), 1.90–2.10 (m, 2H), 4.39 (t, J = 7.0 Hz, 2H), 7.36–7.42 (m, 1H), 7.47–7.52 (m, 1H), 7.57–7.64 (m, 1H), 7.97–8.10 (m, 1H); ^{13}C NMR δ 13.9, 22.3, 26.1, 29.3, 31.1, 48.6, 110.1, 115.7, 124.1, 130 (2C), 133.9. Anal. Calcd for $C_{12}H_{17}N_3O$: H, 7.81; N, 19.16. Found: H, 8.21; N, 19.14. HRMS Calcd for $C_{12}H_{17}N_3O$ (M+1): 220.1450. Found: 220.1441

3-Nonyl-3*H*-1,2,3-benzotriazole 1-oxide (3.5e). White prisms (90%) (from ethyl acetate/hexanes); mp: 77–78 °C; ^{1}H NMR δ 0.87 (t, J = 6.6 Hz, 3H), 1.16–1.40 (m, 12H), 1.90–2.08 (m, 2H), 4.38 (t, J = 7.08 Hz, 2H), 7.30–7.40 (m, 1H), 7.41–7.48 (m, 1H), 7.57–7.70 (m, 1H), 8.00 (d, J = 8.7 Hz, 1H); ^{13}C NMR δ 14.0, 22.5, 26.5, 28.9, 29.1, 29.2, 29.3, 31.7, 48.6, 110.1, 115.7, 124.1, 130 (2C), 133.9. Anal. Calcd for $C_{15}H_{23}N_3O$: C, 68.93; H, 8.87; N, 16.08. Found: C, 69.16; H, 9.38; N, 16.14.

3-Benzyl-3*H*-1,2,3-benzotriazole 1-oxide (3.5f). White prisms (92%) (from ethyl acetate/hexanes); mp: 130–132 °C; ^{1}H NMR δ 5.56 (s, 2H), 7.30–7.40 (m, 7H), 7.49–7.57 (m, 1H), 7.97 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 52.6, 110.6, 115.7, 124.2, 127.7 (2C), 128.8, 129.1 (2C), 130.3, 130.7, 133.65, 133.7. Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.23; H, 5.22; N, 18.71.

3-(2-Phenylethyl)-3*H*-1,2,3-benzotriazole 1-oxide (3.5g). Brown prisms (92%) (from ethyl acetate/hexanes); mp: 150–152 °C; ^{1}H NMR δ 3.24 (t, J = 7.0 Hz, 2H), 4.59 (t, J = 7.0 Hz, 2H), 7.04–7.12 (m, 3H), 7.16–7.24 (m, 3H), 7.26–7.34 (m, 1H), 7.38–7.46 (m, 1H), 7.92 (d, J = 8.2 Hz, 1H); ^{13}C NMR δ 36.0, 50.1, 109.9, 115.5, 123.9, 127.1, 128.6 (2C), 128.8 (2C), 130.0 (2C), 134.2, 136.8. Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.53; H, 5.67; N, 17.74.

3-(1-Phenylethyl)-3*H*-1,2,3-benzotriazole 1-oxide (3.5h). Brown prisms (73%) (from ethyl acetate/hexanes); mp: 139–140 °C; ^{1}H NMR δ 2.06 (d, J = 7.0 Hz, 3H), 5.78 (q, J = 7.0 Hz, 1H), 7.20–7.39 (m, 7H), 7.40–7.46 (m, 1H), 7.96 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 20.9, 59.7, 110.9, 115.7, 124.3, 126.3 (2C), 128.7, 129.1 (2C), 130.0, 130.6, 133.4, 139.1. Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.27; H, 5.48; N, 17.56. Found: C, 69.91; H, 5.81; N, 17.36.

3-(2-Ethoxy-2-oxoethyl)-3*H*-1,2,3-benzotriazole 1-oxide (3.5i). White prisms (68%) (from ethyl acetate/hexanes); mp: 125–126 °C; ^{1}H NMR δ 1.26 (t, J = 7.1 Hz, 3H), 4.24 (q, J = 7.1 Hz, 2H), 5.16 (s, 2H), 7.37–7.42 (m, 1H), 7.47 (d, J = 8.7 Hz, 1H), 7.59–7.67 (m, 1H), 7.98 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 13.9, 48.9, 62.5, 110.3, 115.7, 124.3, 130.7 (2C), 134.7, 165.7. Anal. Calcd for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.47; N, 18.99. Found: C, 54.22; H, 5.32; N, 18.86.

3-(1-Phenoxymethyl)-3*H*-1,2,3-benzotriazole 1-oxide (3.5j). Off-white prisms (91%) (from ethyl acetate/hexanes), mp: 128–129 °C; ^{1}H NMR δ 6.26 (s, 2H), 7.00–7.10 (m, 3H), 7.22–7.34 (m, 2H), 7.38–7.46 (m, 1H), 7.63 (d, J = 3.8 Hz, 2H), 7.97 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 75.0, 110.9, 115.8, 116.3 (2C), 123.4, 124.8, 129.9 (2C), 131.0 (2C), 134.0, 155.8. Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.46; H, 4.59; N, 17.25.

3-(2-Propynyl)-3*H*-1,2,3-benzotriazole 1-oxide (3.5k). White prisms (35%) (from ethyl acetate/hexanes); mp: 159–160 °C; ^{1}H NMR δ 2.56 (t, J = 2.4 Hz, 1H), 5.20 (d, J = 2.4 Hz, 2H), 7.38–7.46 (m, 1H), 7.60–7.72 (m, 2H), 7.98 (d, J = 8.5 Hz, 1H); ^{13}C NMR δ 38.4, 74.4, 75.8, 110.8, 115.8, 124.5, 130.6 (2C), 133.7. Anal. Calcd for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.26. Found: C, 62.17; H, 4.10; N, 24.04.

3-(Cyanomethyl)-3*H*-1,2,3-benzotriazole 1-oxide (3.5l). White needles (40%) (from ethyl acetate/hexanes); mp: 172–173 °C; ^{1}H NMR δ 5.34 (s, 2H), 7.45–7.51 (m, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.70–7.80 (m, 1H), 8.04 (d, J = 8.5 Hz, 1H); ^{13}C NMR δ 36.9, 110.2, 112.5, 115.0, 124.4, 130.3, 130.8, 133.6. Anal. Calcd for $C_8H_6N_4O$: C, 55.17; H, 3.47. Found: C, 54.92; H, 3.59.

Oxidation of 1-allyl-1*H*-benzotriazole (3.4n). 1-Allylbenzotriazole (0.40 g, 2.5 mmol) was placed in a dry flask, dissolved in 0.3 M solution of DMD (2.5 mmol, 8.3 mL) in CH_2Cl_2 and kept at 0 °C for 24 h. The reaction was monitored by TLC. The mixture was warmed up to rt. and kept for 6 h. Another portion of DMD (4.1 mL, 1.2 mmol) was added. After the disappearance of the starting material the solvent was removed to give a mixture of **3.6** and **3.7** as brown oil, the components were separated by column chromatography on silica gel using 25 to 30% acetone in pentane, as an eluent.

1-(2-Oxiranylmethyl)-1*H*-1,2,3-benzotriazole (3.6). Yellow oil (46%); ^{1}H NMR δ 2.26 (bs, 1H), 2.90 (t, J = 3.6 Hz, 1H), 3.38–3.46 (m, 1H), 4.57 (dd, J = 15.0, 6.0 Hz, 1H), 5.09 (dd, J = 15.0, 1.9 Hz, 1H), 7.32–7.42 (m, 1H), 7.44–7.54 (m, 1H), 7.67 (d, J = 8.2 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H); ^{13}C NMR δ 45.0, 50.1, 50.2, 109.9, 119.6, 123.9, 127.5, 133.3, 145.8. Anal. Calcd for $C_9H_9N_3O$: N, 23.99. Found: N, 23.75.

3-(2-Oxiranylmethyl)-3*H*-1,2,3-benzotriazole 1-oxide (3.7). Yellow prisms (29%) (from acetone/pentane); mp: 85.5–87.0 °C; ^{1}H NMR δ 2.71 (t, J = 2.3 Hz, 1H), 2.90–2.98 (m, 1H), 3.37–3.46 (m, 1H), 4.37 (dd, J = 15.1, 6.2 Hz, 1H), 4.82 (dd, J = 15.1, 2.4 Hz, 1H), 7.35–7.45 (m, 1H), 7.56–7.70 (m, 2H), 7.95 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 45.2, 49.8, 50.7, 111.1, 115.3, 124.4, 130.3, 130.5, 134.5. Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98. Found: C, 56.33; H, 4.97; N, 21.82.

Deoxygenation of 3-nonyl-3*H*-1,2,3-benzotriazole 1-oxide (3.5e). 3-Nonyl-3*H*-1,2,3-benzotriazole 1-oxide (0.10 g, 0.38 mmol) was dissolved in Ac_2O (5 mL) and heated under reflux for 48 h. The excess acetic anhydride was destroyed by treatment with water. The cooled mixture was extracted with CH_2Cl_2, washed with aqueous Na_2CO_3 (sat. solution). The organic layer was dried over $MgSO_4$. Evaporation of the solvent produced yellow oil that appears to have NMR spectra and R_f on TLC identical with those for compound **3.4e**.

Deprotonation of 3-nonyl-3*H*-1,2,3-benzotriazole 1-oxide (3.5e). 3-Nonyl-3*H*-1,2,3-benzotriazole 1-oxide (0.10 g, 0.38 mmol) was dissolved in dry THF (10 mL), cooled to –78 °C and a 2 M solution of LDA (0.23 mL, 0.46 mmol) was added dropwise. The mixture was kept for 15 min at this temperature before D_2O (2 mL) was added. The mixture was allowed to warm up to rt., the organic phase was separated, dried over $MgSO_4$ and evaporated to give a brown oil as a mixture of compounds **3.9** (90%) and **3.10**. The NMR spectrum was recorded for the oil obtained.

7-Deuterio-3-nonyl-1*H*-1,2,3-benzotriazole 1-oxide (3.9): ^{1}H NMR δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.16–1.40 (m, 12H), 1.90–2.08 (m, 2H), 4.38 (t, *J* = 7.1 Hz, 2H), 7.38 (d, *J* 6.9 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.54–7.66 (m, 1H); ^{13}C NMR δ 14.0, 22.6, 26.5, 28.9, 29.1, 29.2, 29.3, 31.8, 48.6, 110.1, 115.6 (t, *J* = 26.3), 124.0, 130.1 (2C), 133.9.

3-(1-Deuteriononyl)-1*H*-1,2,3-benzotriazole 1-oxide (3.10): ^{1}H NMR δ0.87 (t, *J* = 6.6 Hz, 3H), 1.16–1.40 (m, 12H), 1.90–2.08 (m, 2H), 4.38 (t, *J* = 7.1 Hz, 1H), 7.30–7.40 (m, 1H), 7.41–7.48 (m, 1H), 7.57–7.70 (m, 1H), 8.00 (d, *J* = 8.7 Hz, 1H).

Synthesis of 1-(trimethylsilyloxy)-3-benzyl-3*H*-1,2,3-benzotriazolium trifluoromethanesulfonate (3.11). 3-Benzyl-3*H*-1,2,3-benzotriazole 1-oxide (**3.5f**)

(0.05 g, 0.22 mmol) was dissolved in $CDCl_3$ (0.7 mL) in an NMR tube, trimethylsilyl trifluoromethanesulfonate (0.04 mL, 0.24 mmol) was added at rt.; the tube was shaken well, and kept for 30 min before NMR spectra were recorded. An attempt to isolate the neat compound **3.11** by evaporation of $CDCl_3$ led to brown oil. ^{1}H NMR δ 5.95 (s, 2H), 7.34–7.50 (m, 5H), 7.72–7.88 (m, 3H), 7.98–8.04 (m, 1H); ^{13}C NMR δ 55.7, 113.3, 113.2, 128.6, 129.5, 129.9, 130.4, 130.8, 131.1, 132.3, 133.9.

2-(2-Phenylethyl)-*trans*-4,5,6,7-diepoxy-4,5,6,7-tetrahydrobenzotriazole (3.13a). This compound was prepared according to the general procedure (method B) except that 2 equivalent of DMD was used. After 48 h, the solvent was removed and another 2 equivalent DMD solution was added. After 24 h, the solvent was removed, the product was purified by column chromatography using ether and pentane as an eluent to give a yellow oil (50%); ^{1}H NMR δ 3.24 (t, J = 7.8 Hz, 2H), 3.89 (m, J = 4.0,1.4 Hz, 2H, 4-H and 7-H), 3.98 (m, J = 4.0, 1.4, 0.7 Hz, 2H, 5-H and 6-H), 4.59 (t, J = 7.8 Hz, 2H), 7.12–7.20 (m, 2H), 7.20–7.34 (m, 3H); ^{13}C NMR δ 36.1, 45.4 (2C), 53.9 (2C), 56.4, 126.9, 128.6 (2C), 128.7 (2C), 137.0, 140.8 (2C); Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.76; H, 5.23; N, 16.57.

2-(2-*p*-Nitrophenylethyl)-*trans*-4,5,6,7-diepoxy-4,5,6,7-tetrahydrobenzotriazole (3.13b). White amorphous solid (77%), mp: 171–173 °C; ^{1}H NMR δ 3.38 (t, J = 7.3 Hz, 2H), 3.89 (ddd, J = 4.0, 1.4, 0.7 Hz, 2H, 4-H and 7-H), 4.00 (ddd, J = 4.0, 1.4, 0.7 Hz, 2H, 5-H and 6-H), 4.67 (t, J = 7.3 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 8.15 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 35.6, 45.3 (2C), 53.9 (53.9), 55.4, 124.0 (2C), 129.2, 129.5(2C), 141.2 (2C), 144.7; Anal. Calcd for $C_{14}H_{12}N_4O_4$: C, 56.00; H, 4.03.

Found: C, 56.02; H, 4.00. HRMS Calcd for $C_{14}H_{12}N_4O_4$ (M+1): 301.0937; Found: 301.093.

CHAPTER 4
SYNTHESIS AND REACTIONS OF BENZOTRIAZOLYL EPOXIDES

4.1 Introduction

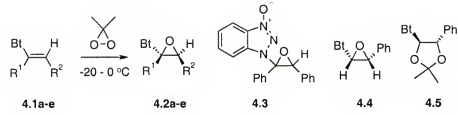
Epoxides are important in organic synthesis due to their high reactivity [1983T2323], [1984S629]. Since Eisch and Galle [1990JOC4835] reported the deprotonation of α-heterosubstituted epoxides, oxiranyllithium compounds have become important synthetic intermediates. Phenylsulphonyl [1991JCS(P1)897] and benzothiazolyl [1993TL1363] groups were used to stabilize the oxiranyl anion successfully in the functionalization of epoxides. A series of α-benzotriazolyl epoxides was previously synthesized in yields of 43 to 80% from 1-substituted 1-(benzotriazolyl)alkenes by oxidation with *m*-CPBA and subsequently converted into the corresponding α-hydroxy ketones [1996SC2657].

In the previous chapter, we demonstrated the dimethyldioxirane (DMD) conversion of 1-alkylbenzotriazoles into 3-alkylbenzotriazole 1-oxides [2001JOC5585]. We now report the efficient and almost quantitative low temperature conversion by dimethyldioxirane of vinylbenzotriazoles into their epoxides together with some of their reactions including reactions with nucleophiles and the deprotonation of α-benzotriazole substituted epoxides.

4.2 Results and Discussion

Synthesis of α-benzotriazolyl epoxides. A solution of DMD in CH_2Cl_2 (0.2 to 0.4 M) [1991CB2377], [1997T8643] converted vinylbenzotriazoles **4.1a-d** into the

corresponding epoxides **4.2a-d**; simple removal of the solvent gave the products in 96-99% yields (Scheme 4-1; Table 4-1). The reactions of nonfunctionalized alkenes or those bearing electron donor groups were complete in less than an hour at −20 °C; but when R^2 was a phenyl group, the reaction took 8 to10 h at 0 °C. Compound **4.1e**, where both R^1 and R^2 were phenyl groups, was consumed only after 30 h at 0 °C; **4.1e** was the only vinylbenzotriazole to undergo non-stereoselective oxidation to give the corresponding epoxide **4.2e** (52%) along with the 1-benzotriazolyl 3-*N*-oxide substituted epoxide **4.3** (34%) (Scheme 4-1).



4.1a-e **4.2a-e** **4.3** **4.4** **4.5**

a: $R^1 = R^2 = H$
b: $R^1 = CH_3$, $R^2 = H$
c: $R^1 = H$, $R^2 = CH_3$
d: $R^1 = H$, $R^2 = Ph$
e: $R^1 = R^2 = Ph$

Scheme 4-1

Table 4-1. Synthesis of α-benzotriazolyl epoxides **4.2**

Epoxides	R^1	R^2	Time (h)	Temp (°C)	Yield (%)
4.2a	H	H	0.5	-20	99
4.2b	CH_3	H	0.1	-20	97
4.2c	H	CH_3	0.1	-20	99
4.2d	H	Ph	10	0	99
4.2e	Ph	Ph	30	0	52

Compounds **4.1a-d** reacted with DMD exclusively at the C=C bond to give epoxides, but not at the N-3 atom of the benzotriazole ring. This can be explained by the relative energies of the two MO's localized mainly on the C=C bond and on the N-3

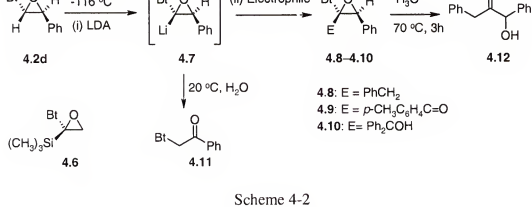
atom. According to a study of the electronic structure of 1-vinyl-1*H*-benzotriazoles [1999JMS47], the energy of the MO of the C=C bond is higher than that of those localized on N-3. The order of these two MOs here is reversed compared to that of 1-allylbenzotriazole, which is oxidized to the 3-*N*-oxides [2001JOC5585].

The stereochemistry of the olefins was preserved during oxidations below 0 °C: *trans*-olefins **4.1c** and **4.1d** gave *trans*-epoxides **4.2c** and **4.2d,** respectively. The *trans*-stereochemistry of the epoxides **4.2c** and **4.2d** was deduced from the vicinal coupling constant (1.5 Hz or less) that is in agreement with the literature data for *J* values (0–1.7 Hz) for 1-aryl-2-phenyl epoxides [1992T2453]. In the ^{1}H NMR spectrum of **4.2c**, the α-H (with respect to Bt) appeared as a doublet at 5.44 ppm with a coupling constant of 1.2 Hz, while the β-H appeared as a doublet of quartets at 4.24 ppm (J = 1.2 and 5.4 Hz), and the methyl group appeared as a doublet at 1.60 ppm (J = 5.4 Hz). In the ^{1}H NMR spectrum of **4.2d**, two epoxide protons were observed at 5.11 and 5.69 ppm as doublets with a coupling constant of 1.5 Hz.

A mixture of the *cis* (40%) and *trans* (60%) isomers of **4.1d** reacted with 1.5 equiv of DMD to give three isolated products: the *trans*-epoxide **4.2d** (52%), the *cis*-epoxide **4.4** (28%) and the 1,3-dioxolane **4.5** (1.4%) (Scheme 4-1). The *cis*-stereochemistry of **4.4** was confirmed by the ^{1}H NMR spectrum, in which two doublets of integral intensity of 1H were observed at 5.82 ppm (J = 2.6 Hz) and 4.58 ppm (J = 2.6 Hz). In the ^{1}H NMR spectrum of **4.5**, two methyl groups appeared as singlets at 1.83 and 1.88 ppm; the dioxolane protons appeared as doublets at 6.40 and 6.61 ppm with a coupling constant of 6.1 Hz. The *trans*-stereochemistry of **4.5** was assigned by comparing the ^{1}H NMR spectrum to literature data [1996TL115]. The coupling constant

is slightly smaller than that of a similar type of dioxolane (J = 8.5 Hz) [1996TL115] due to the presence of the electron-withdrawing benzotriazole group.

Deprotonation of α-benzotriazolyl epoxides and subsequent reactions with electrophiles. Treatment of the simplest benzotriazolyl epoxide **4.2a** with LDA at −78 °C, followed by the addition of MeI failed to give any coupling product. When Me_3SiCl was used at −116 °C, the anion generated *in situ* from **4.2a** by LDA, was captured to give the expected product **4.6** in 30% isolated yield. This proved the formation of an oxiranyllithium species that is stabilized by benzotriazole. Treatment of epoxide **4.2d** with fresh LDA at −116 °C, followed by the immediate addition of electrophile $PhCH_2Br$, afforded epoxide **4.8** in 51% yield along with the rearranged product **4.11** (Scheme 4-2). The generation of oxiranyllithium **4.7** from **4.2d** by LDA is very fast at −116 °C; **4.7** is stable at and below this temperature for about 5 to 20 minutes. As the temperature goes above −110 °C, the anion starts to undergo rearrangement to give compound **4.11**, which is the major product when the LDA is not freshly prepared. The rearrangement product **4.11** was the only product, when **4.2d** was treated with LDA at −116 °C, and allowed to warm up to 20 °C. The oxiranyllithium **4.7** reacts with a



Scheme 4-2

strong electrophile *p*-toluoyl chloride to give coupling product **4.9** in 56% yield; it also reacts with a hindered ketone, benzophenone, to give oxiranyl alcohol **4.10** in 52% yield (Table 4-2).

Table 4-2. The coupling reactions of oxiranyllithium **4.7** from **4.2d** with electrophiles

Product	Electrophile	E	Yield (%)
4.8	$PhCH_2Br$	$PhCH_2$	51
4.9	p-$CH_3C_6H_4COCl$	p-$CH_3C_6H_4C{=}O$	56
4.10	$Ph_2C{=}O$	Ph_2COH	52

Reactions with Nucleophiles. We next examined the possible replacement of the benzotriazole group in epoxides **4.2** by nucleophiles, which could be activated by an α-oxygen atom. The reaction of Grignard reagent $PhCH_2MgCl$ with **4.2a** or **4.2d** at −30 to −18 °C gave complex mixtures. When trisubstituted epoxide **4.8** was treated with $PhCH_2MgCl$ or with organozinc reagent $PhCH_2ZnCl$ in THF and diethyl ether, the starting material was recovered unreacted.

Well-documented literature precedence [1986T5607] exists for the nucleophilic ring opening of epoxides. Epoxides **4.8–4.10** were reluctant to ring open under the acidic conditions used previously [1996SC2657], [1970T825]. Epoxide **4.8** was hydrolyzed to give 1-hydroxy-1,3-diphenylpropan-2-one **4.12** (50%) on heating neat in 6 M sulfuric acid solution at 70 °C for 3 h (Scheme 4-2). Epoxide **4.9** survived under these conditions, but decomposed when refluxed in THF with 30% $HClO_4$ for 24 h [1996SC2657]. Epoxide **4.10** was unaffected by refluxing in 6 M sulfuric acid solution over 5 h or in THF with 30% $HClO_4$ for 36 h.

To conclude, dimethyldioxirane converts 1- and 2-substituted 1-(benzotriazol-1-yl)alkenes into the corresponding epoxides in almost quantitative yields. The rate of

epoxidation decreases for alkenes with electron-withdrawing substituents. A benzotriazole group effectively stabilizes oxiranyl anion at temperatures below –116 °C, thus allowing various functionalization of the epoxides.

4.3 Experimental

General. Melting points were determined on a MEL-TEMP® capillary melting point apparatus equipped with a Fluke 51 digital thermometer, and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz in $CDCl_3$ and referenced to Me_4Si for the ^{1}H spectra and $CDCl_3$ for the ^{13}C spectra. Tetrahydrofuran was distilled under nitrogen from sodium-benzophenone immediately before use. All reactions with moisture-sensitive compounds were carried out in dry argon atmosphere. Substituted 1-(1-ethenyl)benzotriazoles were prepared according to previously reported procedures [1988RTC641]. Dimethyldioxirane solutions were prepared as described previously [1991CB2377], [1997T8643].

General procedure for the oxidation of vinylbenzotriazoles 4.1a-d. Vinylbenzotriazole **4.1** was placed in a dry flask, dissolved in 1.5 M equivalent of DMD solution in dichloromethane and kept at –20 °C. The reaction was monitored by TLC. The removal of the solvent afforded the product in quantitative yield.

2-(Benzotriazol-1-yl)oxirane (4.2a). Beige plates (from CH_2Cl_2) (100%); mp: 48.5–50.0 °C; ^{1}H NMR δ 3.42 (dd, J = 4.4, 3.1 Hz, 1H), 4.40 (dd, J = 4.4, 1.6 Hz, 1H), 5.69 (dd, J = 3.1, 1.6 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.1 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 46.0, 60.3, 109.6, 120.4, 124.7,

128.4, 132.5, 145.7. Anal. Calcd for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.58; H, 4.38; N, 25.86.

2-(Benzotriazol-1-yl)-2-methyloxirane (4.2b). Yellow oil (97%); ^{1}H NMR δ 2.14 (s, 3H), 3.27 (d, J = 4.5 Hz, 1H), 3.63 (d, J = 4.5 Hz, 1H), 7.34–7.44 (m, 1H), 7.46–7.54 (m, 1H), 7.76 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 8.2 Hz, 1H); ^{13}C NMR δ 20.8, 53.1, 68.3, 110.8, 120.0, 124.3, 127.9, 131.8, 145.9. Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18. Found: C, 61.62; H, 5.43

***trans*-2-(Benzotriazol-1-yl)-3-methyloxirane (4.2c).** White prisms (from ether/pentane) (99%); mp: 66–67 °C. ^{1}H NMR δ 1.60 (d, J = 5.3 Hz, 3H), 4.24 (q, J = 5.3 Hz, 1H), 5.44 (s, 1H), 7.36–7.44 (m, 1H), 7.46–7.78 (m, 1H), 7.66 (d, J = 8.2 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 16.3, 54.1, 66.0, 109.8, 120.2, 124.5, 128.2, 132.7, 146.2. Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.93; H, 5.23; N, 23.97.

***trans*-2-(Benzotriazol-1-yl)-3-phenyloxirane (4.2d).** White prisms (from ether/pentane) (96%); mp: 83–84 °C; ^{1}H NMR δ 5.10 (d, J =1.5 Hz, 1H), 5.68 (d, J = 1.5 Hz, 1H), 7.40–7.49 (m, 6H), 7.54–7.59 (m, 1H), 7.75 (d, J = 8.5 Hz, 1H), 8.12 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 57.7, 67.5, 109.8, 120.4, 124.7, 126.0 (2C), 128.4, 128.9 (2C), 129.4, 132.7, 133.6, 146.3. Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.89; H, 4.65; N, 17.73.

***cis*-2-(Benzotriazol-1-yl)-3-phenyloxirane (4.4).** White needles (from ether/pentane) (30%); mp: 103–104 °C; ^{1}H NMR δ 4.57 (d, J = 2.7 Hz, 1H), 5.82 (d, J = 2.7 Hz, 1H), 7.02–7.18 (m, 5H), 7.29–7.37(m, 1H), 7.40–7.48 (m, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 58.6, 65.9, 110.5, 119.9, 124.2, 126.4 (2C),

127.9, 128.2 (2C), 128.8 131.2, 133.4, 145.2. Anal. Calcd for $C_{14}H_{11}N_3O$: C 70.87; H, 4.67; N, 17.71. Found: C, 70.89; H, 4.65; N, 17.73. Found: C, 70.57; H, 4.58; N, 17.59.

***trans*-2,2-Dimethyl-4-(benzotriazol-1-yl)-5-phenyl-1,3-dioxolane (4.5).** White prisms (from ether/pentane) (1.4%); mp: 147–149 °C; ^{1}H NMR δ 1.83 (s, 3H), 1.88 (s, 3H), 6.40 (d, J = 6.1 Hz, 1H), 6.61 (d, J = 6.1 Hz, 1H), 7.40–7.62 (m, 6H), 7.63–7.72 (m, 1H), 7.78 (d, J = 8.2 Hz, H), 8.26 (d, J = 8.2 Hz, H); ^{13}C NMR δ 26.4, 27.8, 80.3, 90.6, 110.3, 112.9, 120.5, 124.8, 126.4, 128.3, 129.1, 129.2, 133.7, 137.1, 146.8. Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.17; H, 5.37; N, 13.90.

Procedure for oxidation of vinylbenzotriazole 4.1e. 4.1e (1.5 g, 5.04 mmol) was dissolved in dimethyldioxirane solution in dichloromethane (0.22 M, 28 mL, 6.05 mmol) and kept at 0 °C. After 18 h, the solvent was removed and another portion of DMD (4.0 mmol, 16 mL, 0.27 M) was added. After another 12 hours, the solvent was removed to give yellow oil. The product was purified by column chromatography using diethyl ether and pentane to give **4.2e** and **4.3.**

2-(Benzotriazol-1-yl)-2,3-diphenyloxirane (4.2e). White prisms (from ether/pentane, 52%); mp: 132–133 °C; ^{1}H NMR δ 4.64 (s, H), 6.96–7.02 (m, 2H), 7.08–7.25 (m, 3H), 7.24–7.28 (m, 3H), 7.30–7.48 (m, 4H), 7.63 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 8.2 Hz, 1H); ^{13}C NMR δ 68.5, 74.4, 110.6, 120.0, 124.2, 125.4 (2C), 126.1 (2C), 128.1, 128.2 (2C), 128.9 (2C), 128.9, 129.6, 132.4, 133.6, 135.2, 145.2. Anal. Calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.40; H, 4.67; N, 13.54.

2-(Benzotriazol-1-yl-3-oxide)-2,3-diphenyloxirane (4.3). White prisms (from ether/pentane) (34%); mp: 145–147 °C; ^{1}H NMR δ 4.56 (s, 1H), 7.10–7.26 (m, 5H), 7.32–7.44 (6H), 7.50–7.58 (m, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.7 Hz, 1H);

^{13}C NMR δ67.9, 74.6, 118.8, 115.6, 124.6, 125.3 (2C), 126.1(2C), 128.4 (2C), 129.0 (2C), 129.3, 130.0, 130.2, 130.9, 131.6, 134.3, 134.6. Anal. Calcd for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 72.82; H, 4.62; N, 12.66.

General procedure for the lithiation of 2-(benzotriazol-1-yl)oxiranes (4.2a and 4.2d). Oxirane **4.2** (1.5 mmol) was placed in an oven dried flask under argon, dissolved in dry THF (10 mL), dry diethyl ether (10 mL) was added as a co-solvent, and the reaction mixture was cooled to –116 °C with stirring. To this, 1.1 equiv of LDA (fresh) was added dropwise, and immediately after, an electrophile (1.65 mmol) was added dropwise. The reaction mixture was allowed to warm up to room temperature and quenched with water. The reaction mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated to give brown oil, which was purified by column chromatography on silica gel using diethyl ether and pentane.

2-(Benzotriazol-1-yl)-2-trimethylsilyloxirane (4.6). Yellow oil (30%); ^{1}H NMR δ0.21 (s, 9H), 3.19 (d, J = 5.0 Hz, 1H), 3.45 (d, J = 5.0 Hz, 1H), 7.25–7.42 (m, 1H), 7.30–7.52 (m, 1H), 7.68 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H); ^{13}C NMR δ–3.4, 50.0, 64.2, 111.0, 120.0, 124.2, 127.6, 132.6, 145.6.

2-(Benzotriazol-1-yl)-2-benzyl-3-phenyloxirane (4.8). Pale yellow oil (51%); ^{1}H NMR δ3.32 (d, J = 14.6 Hz, 1H), 3.53 (d, J = 14.6 Hz, 1H), 4.75 (s, 1H), 6.75 (d, J = 6.5 Hz, 2H), 6.94–7.10 (m, 3H), 7.22–7.56 (m, 6H), 7.61 (d, J = 7.0 Hz, 2H), 7.95–8.05 (m, 1H); ^{13}C NMR δ36.0, 64.0, 76.0, 110.8, 119.8, 124.1, 126.7 (2C), 127.2, 127.8, 128.3 (2C), 128.8 (2C), 129.0, 129.4 (2C), 132.5, 132.8, 133.7, 145.5. HRMS(FAB) Calcd for $C_{21}H_{17}N_3O$ (M+1): 328.1450. Found: 328.1457.

2-(Benzotriazol-1-yl)-2-*p*-toluoyl-3-phenyloxirane (4.9). White amorphous solid (56%); mp: 118–120 °C; ^{1}H NMR δ2.21 (s, 3H), 5.76 (s, 1H), 7.01 (d, J = 8.0 Hz, 2H), 7.21–7.41 (m, 4H), 7.48–7.56 (m, 3H), 7.71 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 7.5 Hz, 2H), 8.02 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ21.7, 62.8, 74.0, 110.3, 120.2, 124.9, 126.5 (2C), 128.6 (2C), 129.0, 129.3 (2C), 129.4 (2C), 130.5, 130.9, 133.1, 145.8, 146.1, 186.3. Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82 .35; Found: C, 74.04; H, 5.03; N, 11.57.

2-(Benzotriazol-1-yl)-2-(1,1-diphenyl-1-hydroxymethyl)-3-phenyloxirane (4.10). White amorphous solid (52%); mp: 143–145 °C; ^{1}H NMR δ4.50 (s, H), 4.72 (s, H), 6.90–7.10 (m, 10H), 7.25–7.35 (m, 4H), 7.38–7.48 (m, 1H), 7.49–7.54 (m, 2H), 7.84–7.95 (m, 2H); ^{13}C NMR δ64.6, 79.2, 80.8, 112.0, 119.8, 124.3, 126.0 (2C), 126.5 (2C), 127.1, 127.2 (2C), 127.3, 127.4, 127.6 (2C), 127.8 (2C), 128.0 (2C), 128.1, 130.9, 133.2, 140.0, 143.9, 144.7. Anal. Calcd for $C_{27}H_{21}N_3O_2$: C, 77.31; H, 5.05. Found: C, 77.24; H, 5.28.

α-(Benzotriazol-1-yl)acetophenone (4.11). This compound was obtained from **4.2d** following the procedure for the lithiation of 2-benzotriazolyloxiranes, except no electrophile was added and the reaction mixture was quenched with water at rt. White plates (from ethyl acetate/hexanes) (80%); mp: 115–117 °C (lit.[1994S597] mp: 115–116 °C): ^{1}H NMR δ6.10 (s, 2H), 7.30–7.80 (m, 6H), 8.01–8.14 (m, 3H); ^{13}C NMR δ59.3, 109.5, 120.1, 124.1, 127.8, 128.3, 129.1, 133.8, 134.0, 134.5, 146.0, 190.3.

Procedure for the hydrolysis of oxirane 4.8. Compound **4.8** (0.18 g, 0.55 mmol) was heated at 70 °C for 3 h with 6 M aqueous solution of H_2SO_4 (30 mL). The reaction mixture was extracted with CH_2Cl_2, washed with a sat. solution of $NaHCO_3$, dried over

$MgSO_4$, and concentrated to give brown oil. The product was purified by column chromatography on silica gel using 25% ethyl acetate in hexane to give 1-hydroxy-1,3-diphenylpropan-2-one **4.12** in 50% yield.

1-Hydroxy-1,3-diphenylpropan-2-one (4.12). White prisms (from ethyl acetate/hexanes) (50%); mp: 114–115 °C (lit.[1991JOC6917] mp: 77–79 °C; lit.[1970BCJ448] mp: 114 °C); ^{1}H NMR δ 3.64 (s, 2H), 4.25 (d, J = 4.5 Hz, H), 5.19 (d, J = 4.5 Hz, H), 6.95–7.05 (m, 2H), 7.20–7.50 (m, 8H); ^{13}C NMR δ 44.6, 79.2, 127.2, 127.7, 128.7, 128.9, 129.1, 129.3, 132.8, 137.5, 206.9.

CHAPTER 5
NEW SYNTHESIS OF 2-BENZAZEPINES

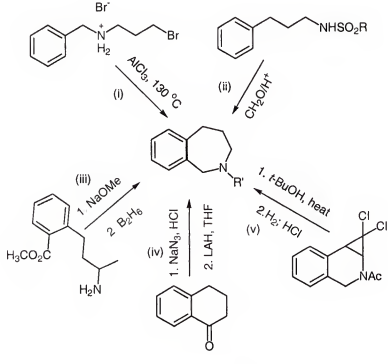
5.1 Introduction

2-Benzazepines [1974AHC45] are of considerable interest due to their diverse pharmacological properties [1979BP528], [1983JMC367], [1983JMC1596]. Known routes to 2-benzazepines include the following (Scheme 5-1): (i) cyclization of *N*-(3-bromopropyl) arylamine hydrobromides with aluminum chloride at 130 °C in decalin [1973JCS(P1)782]; (ii) cyclization of 3-arylpropylsulfonamides with formaldehyde in the presence of acid to the *N*-sulfonyl-2-benzazepine [1986JCS(P1)1977]; (iii) cyclization of 3-(2-methyl carbonyl-aryl)propylamines with sodium methoxide to 2-benzazepin-1-ones and subsequent reduction [1991JHC1587]; (iv) Beckman [1986JHC343] or Schmidt rearrangements of 3,4-dihydro-1(*2H*)-naphthalenone [1982MI1], [1982CA97], [1996JMC3539]; (v) ring enlargement of 2-acetyl-7,8-dichloro-1,2-dihydroisoquinolines [1980JOC1950]. These reactions either uses rather harsh reaction conditions (high temperature, or hazardous materials such as hydrazoic acid), or uses precursors that need multi-step reactions to obtain.

Recently, our group reported syntheses of 1,4-benzothiazepines and 1,4-benzoxazepines from $ArX(CH_2)_2NRCH_2Bt$ (X = O, S) using benzotriazole methodology [2001JOC5590]. In the present work, we now report an analogous approach to 2-benzazepines and explore the possibility of introducing different functional groups onto the benzazepine moiety.

5.2 Results and Discussion

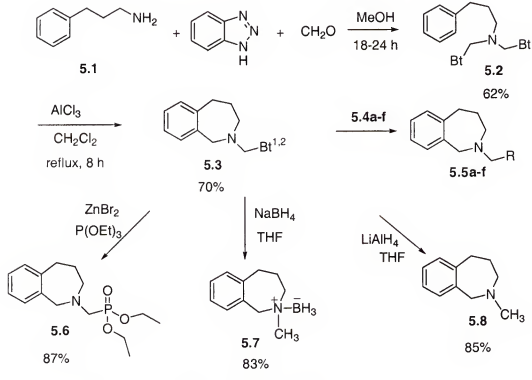
Synthesis of *N,N*-bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)-3-phenyl-1-propanamine (5.2) and cyclization to 2-(1*H*-1,2,3-benzotriazol-1-ylmethyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (5.3). Condensation of 3-phenyl-1-propylamine (**5.1**), benzotriazole and formaldehyde in methanol/water at 20 °C gave pure *N,N*-bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)-3-phenyl-1-propanamine (**5.2**). Compound **5.2** on heating with 4 equiv of $AlCl_3$ in dry CH_2Cl_2 under reflux for 8 to 10 h gave **5.3** in 70% yield (Scheme 5-2). Although the starting material **5.2** was only Bt^1 (benzotriazol-1-yl) isomer, equilibration occurred during the cyclization and product **5.3** was obtained as a mixture of $Bt^1$and Bt^2 (benzotriazol-2-yl) isomers, in which Bt^1 isomer predominated. Preliminary attempts to separate the $Bt^1$and Bt^2 isomers failed. Since both $Bt^1$and Bt^2 can be substituted by nucleophiles, the mixture was used as such in the subsequent reactions.



Scheme 5-1

We have reported the ^{1}H and ^{13}C NMR data of the major Bt^{1} isomer in the experimental section. The ratio of $Bt^{1}$and Bt^{2} isomers was determined by ^{1}H NMR spectrum to be 4.4:1. The aliphatic region in the ^{1}H NMR spectrum of **5.2** showed one strong singlet ascribed to two $BtCH_2N$ at 5.63 ppm. After the cyclization, two singlets were observed at 4.00 ppm and 5.42 ppm in the ^{1}H NMR spectrum of **5.3**, which were ascribed to $ArCH_2N$ and $BtCH_2N$ fragments, respectively.

Reactions of 2-(benzotriazolylmethyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (5.3) with nucleophiles. The benzotriazole moiety in **5.3** could, as expected [1998CRV409], be replaced by various nucleophiles. Thus, reactions of **5.3** with the corresponding Grignard reagents (**5.4a–f**) gave compounds **5.5a–f**, respectively, in 40-70% yields (Scheme 5-2). The results are listed in Table 5-1.



Scheme 5-2

Treatment of compound **5.3** with triethyl phosphite in the presence of $ZnBr_2$ in THF at 0 °C replaced the benzotriazolyl group to give the expected product diethyl 1,3,4,5-tetrahydro-2*H*-2-benzazepin-2-ylmethylphosphonate (**5.6**) in 87% yield (Scheme 5-2).

Table 5-1. Reaction of **5.3** with Grignard reagents

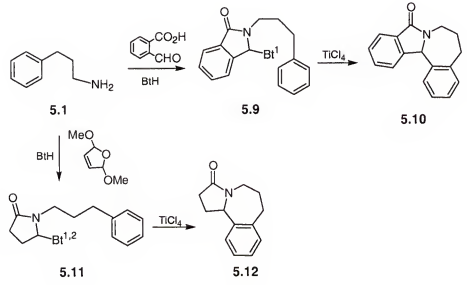
Products **5.5**	Nucleophiles	R	Yields (%)
a	*p*-$MeOC_6H_4MgCl$	*p*-$MeOC_6H_4$	70
b	*p*-ClC_6H_4MgCl	*p*-ClC_6H_4	47
c	$C_6H_5C{\equiv}CMgCl$	$C_6H_5C{\equiv}C$	43
d	CH_3CH_2MgBr	CH_3CH_2	71
e	$CH_3(CH_2)_3MgBr$	$CH_3(CH_2)_3$	69
f	*p*-MeC_6H_4MgCl	*p*-MeC_6H_4	78

The reduction of **5.3** with sodium borohydride in methanol failed; however, compound **5.3** was reduced in THF using sodium borohydride in 4 h at 20 °C to give 2-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine borane complex (**5.7**) in 83% yield (Scheme 5-2). The reduction of **5.3** with lithium aluminumhydride in THF gave 2-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**5.8**) in 85% yield (Scheme 5-2).

Synthesis of 3-(1*H*-1,2,3-benzotriazol-1-yl)-2-(3-phenylpropyl)-1-isoindolinone (5.9), and cyclization to 5,6,7,13b-tetrahydro-9*H*-isoindolo[1,2-*a*][2]benzazepin-9-one (5.10). Heating of 3-phenyl-1-propylamine (**5.1**), benzotriazole and phthalaldehydic acid with a catalytic amount of *p*-toluenesulfonic acid monohydrate using a Dean-Stark apparatus gave 3-(1*H*-1,2,3-benzotriazol-1-yl)-2-(3-phenylpropyl)-1-isoindolinone **5.9** in 89% yield (Scheme 5-3). Heating **5.9** with aluminum chloride in CH_2Cl_2 gave traces of product **5.10**, but $TiCl_4$ (1.7 M solution CH_2Cl_2) afforded the desired 5,6,7,13b-tetrahydro-9*H*-isoindolo[1,2-*a*][2]benzazepin-9-one **5.10** in 83% yield at 20 °C (Scheme 5-3). Compound **5.10** was previously prepared by the cyclization of

3-(3-phenylpropylamine)phthalide in PPA at 95 °C in 30% yield [1972JOC3755].

Synthesis of 5-(1*H*-1,2,3-benzotriazol-1-yl)-1-(3-phenylpropyl)-2-pyrrolidinone (5.11) and cyclization to 1,2,5,6,7,11b-hexahydro-3*H*-pyrrolo[2,1-*a*][2]benzazepin-3-one (5.12). A slightly different procedure from the above, heating of 3-phenyl-1-propylamine (**5.1**), benzotriazole, and 2,5-dimethoxy-2,5-dihydrofuran in acetic acid at 60 °C to 70 °C for 48 h gave **5.11** as mixed Bt^1 and the Bt^2 isomers in 56% yield. Separation by column chromatography afforded the Bt^1 isomer of **5.11** in 47% yield and the Bt^2 isomer of **5.11** in 9% yield (Scheme 5-3). However, the unseparated mixture was used in the subsequent reaction.



Scheme 5-3

Cyclization of **5.11** was more difficult than that for **5.9** using 1.7 M solution of $TiCl_4$, and only a small amount of **5.11** was converted; however, $TiCl_4$ (4 equiv.) in CH_2Cl_2 for 36 h at 20 °C cyclized **5.11** into novel 1,2,5,6,7,11b-hexahydro-3*H*-pyrrolo[2,1-*a*][2]benzazepin-3-one (**5.12**) in 52% yield (Scheme 5-3). No previous examples of the ring system of **5.12** were located.

5.3 Conclusions

In conclusion, we have developed a new approach to 2-benzazepines via cyclization of *N,N*-bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)-3-phenyl-1-propanamine (**5.2**), 3-(1*H*-1,2,3-benzotriazol-1-yl)-2-(3-phenylpropyl)-1-isoindolinone (**5.9**), and 5-(benzotriazolyl)-2-(3-phenylpropyl)-2-pyrrolidinone (**5.11**). A series of *N*-substituted 2-benzazepines were obtained by nucleophilic substitution of benzotriazolyl moiety in **5.3** using different nucleophiles.

5.4 Experimental

Melting points were determined on a Koefler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, in $CDCl_3$ referenced to Me_4Si for the ^{1}H spectra and $CDCl_3$ for the ^{13}C spectra. Tetrahydrofuran was distilled under nitrogen from sodium-benzophenone immediately before use. CH_2Cl_2 was distilled over CaH_2 under nitrogen. Column chromatography was performed on silica gel (200 to 425 mesh, Fisher Scientific). All reactions with moisture-sensitive compounds were carried out in a dry argon atmosphere.

***N,N*-Bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)-3-phenyl-1-propanamine (5.2)** 3-Phenyl-1-propylamine (5 g, 37 mmol) and benzotriazole (9.6 g, 81.2 mmol) were dissolved in methanol (60 mL) and water (15 mL), formaldehyde (6.47 g, 81.4 mmol, 37% aqueous solution) was added. The reaction mixture was stirred for 24 h at 20 °C. Then, the white precipitates were filtered and washed with ether to give the desired product (9.2 g, 62%), which was directly used in the subsequent reaction without further purification. Pale yellow prisms (from ethyl acetate/hexane); yield 62%; mp: 84–86 °C; ^{1}H NMR δ 1.89 (quintet, 2H, J = 7.2 Hz), 2.50 (t, J = 7.2 Hz, 2H), 2.87 (t, J = 7.2 Hz,

2H), 5.63 (s, 4H), 7.01 (d, J = 6.3 Hz, 2H), 7.14–7.26 (m, 3H), 7.41 (dt, J = 0.9, 7.5 Hz, 2H), 7.51 (dt, J = 0.9, 6.9 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 8.4 Hz, 2H). ^{13}C NMR δ 29.1, 32.8, 50.1, 64.4, 109.7, 120.0, 124.2, 126.0, 127.9, 128.2, 128.4, 133.2, 141.1, 146.0. Anal. Calcd for $C_{23}H_{23}N_7$: C, 69.50; H, 5.83; N, 24.67. Found: C, 69.56; H, 5.88; N, 25.02.

2-(Benzotriazolylmethyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (5.3). $AlCl_3$ (0.53 g, 16 mmol) was placed in a dry flask under argon with a stirring bar, a solution of the starting material **5.2** (1.59 g, 4 mmol) in dry CH_2Cl_2 (80 mL) was added and stirred. This mixture was heated under reflux for 8 to 10 h; then, cooled to room temperature and quenched with 2 M NaOH solution (10 mL). The organic layer was separated and washed with 2 M NaOH solution and water. The organic layer was collected and dried over $MgSO_4$. The removal of the solvent gave pale yellow oil (0.23 g, 70%). This oil was used in the next step without purification. ^{1}H NMR δ 1.83 (quintet, J = 5.1 Hz, 2H), 2.89 (t, J = 5.4 Hz, 2H), 3.19 (t, J = 5.1 Hz, 2H), 4.00 (s, 2H), 5.42 (s, 2H), 7.10–7.20 (m, 4H), 7.34–7.56 (m, 2H), 7.65 (d, J = 8.1 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 26.7, 35.4, 57.1, 58.2, 68.1, 110.3, 119.9, 123.9, 126.2, 127.3, 127.6, 129.2, 129.7, 133.2, 138.3, 142.5, 146.1. Anal. Calcd for $C_{17}H_{18}N_4$: N, 20.13. Found: N, 20.49. HRMS (FAB) Calcd for $C_{17}H_{17}N_4$ (M-1): 277.1453. Found: 277.1430.

2-(4-Methoxybenzyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (5.5a); Typical procedure. Compound **5.3** (0.2 g, 0.72 mmol) was dissolved in 10 mL of THF under argon in a round bottom flask with a stirring bar, and cooled to 0 °C in an ice-water bath. After 10 minutes, 4-methoxylbenzylmagnesium bromide (**5.4a**) (0.8 mL, 1.0 M, 0.86 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h. This was

then warmed up to room temperature and stirred for an additional 10 h. The reaction was quenched with 10 mL of water; the organic layer was washed with 2 M NaOH solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, and concentrated to give yellow solid. The product was purified by column chromatography on silica gel using 30% ether in pentane as eluent. Micro-needles (from ether/pentane); yield 70%; mp: 83–85 °C; ^{1}H NMR δ 1.75 (quintet, J = 5.0 Hz, 2H), 2.92 (t, J = 5.1 Hz, 2H), 3.10 (t, J = 5.1 Hz, 2H), 3.46 (s, 2H), 3.81 (s, 3H), 3.86 (s, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 7.2 Hz, 1H), 7.00–7.26 (m, 5H); ^{13}C NMR δ 25.2, 36.2, 55.2, 57.1, 58.7, 59.1, 113.5, 125.8, 127.1, 128.8, 130.0, 130.1, 131.3, 139.4, 143.1, 158.5. Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.43; H, 7.70; N, 5.07.

2-(4-Chlorobenzyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (5.5b). White needles (from ethyl acetate/hexane); yield 47%; mp: 97–99 °C; ^{1}H NMR δ 1.81 (quintet, J = 5.0 Hz, 2H), 2.98 (t, J = 5.0 Hz, 2H), 3.17 (t, J = 5.0 Hz, 2H), 3.54 (s, 2H), 3.90 (s, 2H), 6.96 (d, J = 7.2 Hz, 1H), 7.10–7.24 (m, 2H), 7.25–7.36 (m, 5H); ^{13}C NMR δ 25.2, 36.1, 57.0, 58.9, 59.1, 125.8, 127.2, 128.3, 128.8, 129.9, 130.2, 132.5, 137.9, 139.2, 143.0. Anal. Calcd for $C_{17}H_{18}ClN$: C, 75.13; H, 6.68; N, 5.15. Found: C, 75.32; H, 7.09; N, 5.05.

2-(3-Phenyl-2-propynyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (5.5c). Yellow oil; yield 43%; ^{1}H NMR δ 1.80 (quintet, J = 5.0 Hz, 2H), 2.91 (t, J = 5.0 Hz, 2H), 3.20 (t, J = 5.0 Hz, 2H), 3.52 (s, 2H), 3.98 (s, 2H), 7.08–7.22 (m, 4H), 7.27–7.34 (m, 3H), 7.40–7.50 (m, 2H); ^{13}C NMR δ 26.3, 35.6, 45.8, 58.9, 59.7, 84.7, 85.5, 123.3, 126.1, 127.4, 128.0, 128.2, 128.8, 129.8, 131.7, 138.7, 142.8. Anal. Calcd for $C_{19}H_{19}N$: N, 5.36.

Found: N, 5.67. HRMS (FAB) Calcd for $C_{19}H_{20}N$ (M+1): 262.1596; Found: 262.1601.

2-Propyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (5.5d). Yellow oil; yield 71%; ^{1}H NMR δ0.85 (t, J = 7.2 Hz, 3H), 1.45–1.57 (m, 2H), 1.72 (quintet, J = 5.1 Hz, 2H), 2.28–2.33 (m, 2H), 2.89 (t, J = 5.4 Hz, 2H), 3.12 (t, J = 5.4 Hz, 2H), 3.89 (s, 2H), 7.12 (br s, 4H); ^{13}C NMR δ 11.9, 20.6, 25.0, 36.2, 55.3, 59.0, 59.4, 125.9, 127.1, 128.8, 129.7, 139.3, 142.9. Anal. Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.61; H, 10.45; N, 7.65.

2-Pentyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (5.5e). Brown oil; yield 69%; ^{1}H NMR δ0.87 (t, J = 7.2 Hz, 3H), 1.18–1.34 (m, 4H), 1.46–1.58 (m, 2H), 1.71–1.79 (m, 2H,), 2.36–2.42 (m, 2H), 2.90 (t, J = 6.0 Hz, 2H), 3.15 (t, J = 5.4 Hz, 2H), 3.95 (s, 2H), 7.13 (br s, 4H); ^{13}C NMR δ 14.0, 22.6, 25.0, 27.2, 29.7, 36.2, 53.4, 59.1, 59.5, 125.8, 127.1, 128.7, 129.7, 139.4, 142.9. Anal. Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.44. Found: C, 83.20; H, 11.08; N, 6.76.

2-(4-Methylbenzyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (5.5f). Yellow oil; yield 78%; ^{1}H NMR δ 1.75 (quintet, J = 5.1 Hz, 2H), 2.34 (s, 2H), 2.91(t, J = 5.4 Hz, 2H), 3.10 (t, J = 5.1 Hz, 2H), 3.49 (s, 2H), 3.87 (s, 2H), 6.95 (d, J = 6.9 Hz, 1H), 7.05-7.20 (m, 7H); ^{13}C NMR δ21.1, 25.2, 29.7, 36.1, 57.5, 58.7, 59.2, 125.8, 127.1, 128.7, 128.8, 128.9, 130.0, 136.1, 136.4, 139.4, 143.1. Anal. Calcd for $C_{18}H_{21}N$: C, 86.01; H, 8.42; N, 5.57. Found: C, 86.13; H, 8.37; N, 5.89.

Diethyl 1,3,4,5-tetrahydro-2*H*-2-benzazepin-2-ylmethylphosphonate (5.6). Compound **5.3** (0.1 g, 0.36 mmol) was dissolved in THF (5 mL), cooled to 0 °C in ice-water bath, $ZnBr_2$ (0.08g, 0.36 mmol, oven dried) was added, then, triethyl phosphite (0.07 mL, 0.4 mmol) was added. The mixture was stirred overnight, quenched with

water, extracted with CH_2Cl_2, washed with NaOH (2 M, 2x15 mL), dried over $MgSO_4$. The removal of the solvent gave 0.12 g of oil. The mixture was purified using 5% methanol in chloroform as eluent to give 90 mg of colorless oil (yield 87%). ^{1}H NMR δ 1.32 (t, J = 7.2 Hz, 6H), 1.64–1.74 (m, 2H), 2.72 (d, J = 10.5 Hz, 2H), 2.90 (t, J = 5.1 Hz, 2H), 3.27 (t, J = 5.1 Hz, 2H), 4.06 (s, 2H), 4.06–4.20 (m, 4H), 7.02–7.20 (m, 4H); ^{13}C NMR δ16.5 (d, J = 5.7 Hz), 24.4, 36.1, 47.5 (d, J = 167.2 Hz), 60.2 (d, J = 9.2 Hz), 60.4 (d, J = 8.0 Hz), 62.0 (d, J = 6.9 Hz), 125.9, 127.4, 129.0, 130.4, 138.4, 143.0. Anal. Calcd for $C_{15}H_{24}NO_3P$: C, 60.59; H, 8.14; N, 4.71. Found: C, 60.16; H, 8.51; N, 5.07.

2-Methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine borane complex (5.7). Compound **5.3** (0.28 g, 1 mmol) was dissolved in THF (20 mL), $NaBH_4$ (0.15 g, 4 mmol) was added and stirred at room temperature for 4 h. The solvent was evaporated, the residue was dissolved in dichloromethane, and washed with 2 M NaOH solution. The organic layer was dried over $MgSO_4$ and concentrated to give yellow solid, which was purified by column chromatography on silica gel using 20% ethyl acetate in hexane. Yellow prisms (from ethyl acetate/hexane); yield 83%; mp: 67.6–68.8 °C; ^{1}H NMR δ 1.10–2.10 (m, 5H), 2.32 (s, 3H), 2.78–3.10 (m, 2H), 3.15–3.40 (m, 2H), 4.00 (d, J = 14.7 Hz, 1H), 4.36 (d, J = 14.4 Hz, 1H), 7.15–7.30 (m, 4H). ^{13}C NMR δ23.7, 34.3, 45.2, 65.5, 65.9, 126.8, 128.9, 129.1, 131.6, 132.9, 142.4. Anal. Calcd for $C_{11}H_{18}BN$: C, 74.46; H, 10.36; N, 8.00. Found: C, 75.56; H, 10.22; N, 7.95.

2-Methyl-2,3,4,5-tetrahydro-1H-2-benzazepine (5.8). Compound **5.3** (0.28 g, 1 mmol) was dissolved in THF (20 mL), LAH (0.15 g) was added and stirred at room temperature for 4 h. The solvent was removed, the residue was dissoved in methylene chloride (20 mL), washed with 2 M NaOH solution (3x10 mL), dried (NaSO4), and

concentrated to give yellow oil, which was purified by column chromatography on silica gel using 30% ethyl acetate in hexanes as eluent. Yellow oil; yield 85%; [1997JOC2544]; ^{1}H NMR δ 1.73-1.80 (m, 2H), 2.31 (s, 3H), 2.84-2.90 (m, 2H), 2.96-3.04 (m, 2H), 3.80 (s, 2H), 7.12 (br s, 4H); ^{13}C NMR δ 25.2, 35.5, 42.7, 60.8, 61.6, 126.2, 127.6, 128.9, 130.0, 137.6, 142.7.

3-(1*H*-1,2,3-Benzotriazol-1-yl)-2-(3-phenylpropyl)-1-isoindolinone (5.9). 3-Phenyl-1-propylamine **5.1** (0.3 g, 2.2 mmol), BtH (0.28 g, 2.4 mmol), phthalaldehydic acid (0.34 g, 2.2 mmol) and *p*-toluenesulfonic acid monohydrate (0.04 g, 0.24 mmol) were dissolved in toluene (50 mL) and heated under reflux with a Dean Stark apparatus. After 24 h, the reaction mixture was cooled. After evaporating the solvent, the residue was dissolved in dichloromethane and washed with 2 M NaOH and brine. The organic layer was dried over Na_2SO_4, and concentrated to give yellow oil, which was purified by column chromatography on silica gel using 30% ethyl acetate in hexane as eluent. Yellow flakes (from ethyl acetate/hexane); yield, 89%; mp: 92–93 °C; ^{1}H NMR δ 1.75 (quintet, J = 7.5 Hz, 2H), 2.25 (dt, J = 4.2, 2.7 Hz, 2H), 2.90–3.40 (m, 1H), 3.72–3.84 (m, 1H), 6.40 (d, J = 8.4 Hz, 1H), 7.00 (d, J = 7.2 Hz, 2H), 7.06–7.22 (m, 4H), 7.28–7.36 (m, 2H), 7.38 (s, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 8.04 (d, J = 7.5 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 29.3, 33.0, 40.1, 72.7, 110.0, 120.5, 123.5, 124.2, 124.7, 125.9, 128.1, 128.2, 128.3, 130.5, 130.9, 132.0, 132.9, 138.9, 140.8, 147.0, 167.2. Anal. Calcd for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21. Found: C, 75.12; H, 5.70; N, 15.11.

5,6,7,13b-Tetrahydro-9*H*-isoindolo[1,2-*a*][2]benzazepin-9-one (5.10). Compound **5.9** (0.31 g, 0.84 mmol) was dissolved in CH_2Cl_2 (9 mL), $TiCl_4$ (3.3 mmol,

1.7 M in CH_2Cl_2) was added, and the mixture was stirred at room temperature for 10 h. Then, the reaction was quenched with water. The organic layer was separated, washed with 2 M NaOH, brine, and dried over $MgSO_4$. Removal of the solvent gave yellow solid, which was purified by column chromatography on silica gel using 25% ethyl acetate in hexane as eluent. White micro prisms (from ethyl acetate/hexane); yield 89%; mp: 138–141°C (lit.[1972JOC3755] mp: 143–145 °C); ^{1}H NMR δ 1.84–2.00 (m, 1H), 2.10–2.28 (m, 1H), 2.66–2.76 (m, 2H), 3.31–3.41 (m, 1H), 4.33–4.40 (m, 1H), 5.75 (s, 1H), 7.11–7.14 (m, 1H), 7.23–7.32 (m, 3H), 7.45–7.58 (m, 3H), 7.90 (d, J = 7.2 Hz, 1H); ^{13}C NMR δ 25.4, 31.5, 41.0, 65.8, 123.3, 123.8, 126.8, 127.4, 128.3, 128.4, 130.5, 131.4, 132.2, 135.1, 139.9, 144.0, 168.9.

5-(Benzotriazolyl)-1-(3-phenylpropyl)-2-pyrrolidinone (5.11). 3-Phenyl-1-propylamine **5.1** (1.37 g, 10 mmol), BtH (2.38 g, 20 mmol), 2,5-dimethoxy-2,5-dihydrofuran (1.43 g, 11 mmol) were dissolved in acetic acid (75 mL) and heated at 60–70 °C for 48 h. Then, the reaction mixture was cooled and neutralized with NaOH; extracted with dichloromethane, dried over Na_2SO_4, and concentrated to give yellow oil. The product was separated by column chromatography using 30% to 50% ethyl acetate in hexane as eluent. Yellow oil; yield 56%; ^{1}H NMR δ 1.56–1.84 (m, 2H), 2.34–2.44 (m, 1H), 2.46–2.72 (m, 5H), 2.84–2.96 (m, 1H), 3.54–3.65 (m, 1H), 6.44 (dd, J = 7.9, 2.4 Hz, 1H), 7.03 (d, J = 6.9 Hz, 2H,), 7.10–7.28 (m, 3H), 7.32–7.54 (m, 3H), 8.10 (d, J = 8.1 Hz, 1H,); ^{13}C NMR δ 24.9, 28.0, 29.3, 32.9, 40.4, 72.4, 108.8, 120.5, 124.4, 125.9, 128.0, 128.1, 128.2, 131.2, 140.7, 146.3, 174.3. Anal. Calcd for $C_{19}H_{20}N_4O$: N, 17.49. Found: N, 17.02. HRMS (FAB) Calcd for $C_{19}H_{21}N_4O$ (M+1): 321.1715; Found: 321.1717.

1,2,5,6,7,11b-Hexahydro-3*H*-pyrrolo[2,1-*a*][2]benzazepin-3-one (5.12).

Compound **5.11** (0.4 g, 1.25 mmol) was placed in a dry flask, dissolved in 50 mL of dry CH_2Cl_2, $TiCl_4$ (0.55 mL, 5 mmol) was added and stirred at 20 °C for 36 h. The reaction was quenched with water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with 2 M NaOH, dried over Na_2SO_4, and concentrated to give 0.13 g of brown oil (52%) as the product, no further purification was needed. ^{1}H NMR δ 1.64–1.82 (m, 1H), 1.96–2.10 (m, 1H), 2.12–2.28 (m, 1H), 2.36–2.55 (m, 3H), 2.60–2.74 (m, 1H), 2.87–3.40 (m, 2H), 4.09–4.17 (m, 1H), 4.84 (t, J = 7.2 Hz, 1H), 7.10–7.50 (m, 4H); ^{13}C NMR δ 25.7, 27.9, 31.0, 31.2, 39.6, 64.0, 126.5, 126.7, 127.9, 130.8, 138.6, 139.1, 174.3. HRMS Calcd for $C_{13}H_{16}NO$ (M+1): 202.1232. Found: 202.1175

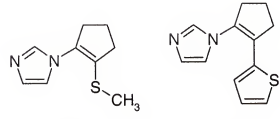
CHAPTER 6
BENZOTRIAZOLE STABILIZED GEMINAL DIANIONS AND THEIR UTILITY IN THE SYNTHESIS OF *N*-CYCLOALKENYL-AZOLES

6.1 Introduction

Molecules containing *N*-cycloalkenyl-heterocycles have potential biological activity, thus 1-[2-(methylsulfanyl)-1-cyclopentenyl]imidazole (**6.I**) and 1-[2-(2-thienyl)-1-cyclopentenyl]imidazole (**6.II**) have been reported as neuronal injury inhibitors (Scheme 6-1) [1998MI1]; however, few synthetic approaches to compounds of this type have been reported. No literature was found for *N*-cycloalkenylpyrroles **6.4a**,**b**. A single paper reported 1-(cyclopent-1-enyl)pyrazole (**6.7a**) and 1-(cyclohex-1-enyl)pyrazole (**6.7b**) which were prepared in 73% and 78% yields, respectively, from the corresponding 1,1-bispyrazolylcycloalkanes [1970JOC3459] (Scheme 6-2, i). 1-Cyclohex-1-enylimidazole (**6.10b**) was formed (9% yield) as a byproduct in the preparation of 1,1-bis(imidazol-1-yl) cyclohexane, which could not be converted into **6.10b** (Scheme 6-2, ii) [1979TL5011]. Compound **6.II** was obtained in 64% using 1-(2-bromocyclopenten-1-yl)imidazole, $(Ph_3P)_4Pd$ and 2-thienylboronic acid with $NaHCO_3$ in DME/H_2O according a German patent [1998MI1] (Scheme 6-2, iii), and the synthesis of **6.I** was described in the same patent document as well.

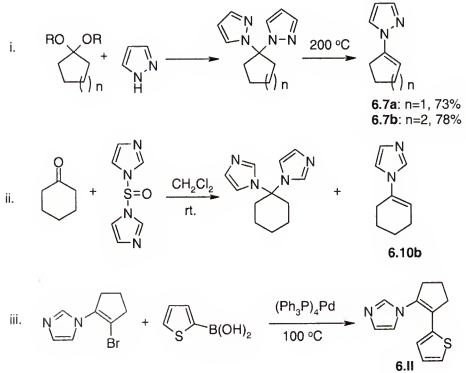
As extensively studied synthetic intermediates [1990MI143], general routes for *N*-vinylpyrroles include the following (Scheme 6-3): (i) cyclization of ketoximes and acetylenes in a strong base-DMSO system [1990MI143]; (ii) vinylation of pyrrole in superbase media [2000S1585]; (iii) reactions of potassium pyrrole with epoxides in dry

DME [1972T1113], [1971TL4321]. 1-Vinylimidazoles were also made from the potassium imidazole and corresponding epoxides [1971TL432], [1976JCS(P1)545]. A recent paper reported the synthesis of *N*-vinyl derivatives of nucleobases via direct vinyl exchange of the acetyl group of vinyl acetate with pyrimidine and purine bases using TMSOTf as acid catalyst [2002S172] (Scheme 6-3, iv). These routes, however, are not normally suitable for the synthesis of *N*-(cycloalkenyl)-pyrroles or -imidazoles.



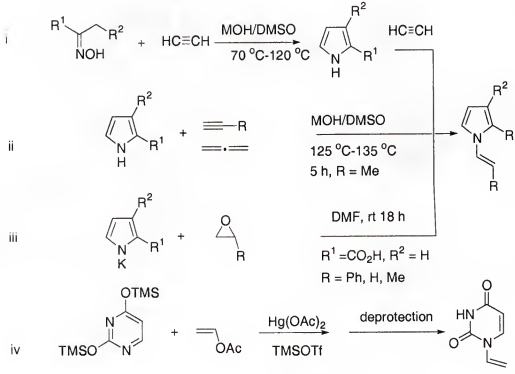
6.I **6.II**

Scheme 6-1



Scheme 6-2

The reactivity and chemoselectivity of geminal dianions (αα-dianions) have been studied [1991T4223]: their existence is supported by deuteriation, and by ^{1}H, and ^{13}C NMR spectroscopy [1985AGE696], and they have been utilized synthetically [1985AGE610]. We now show that benzotriazole stabilized geminal dianions facilitate the synthesis of *N*-cycloalkenyl-azoles.

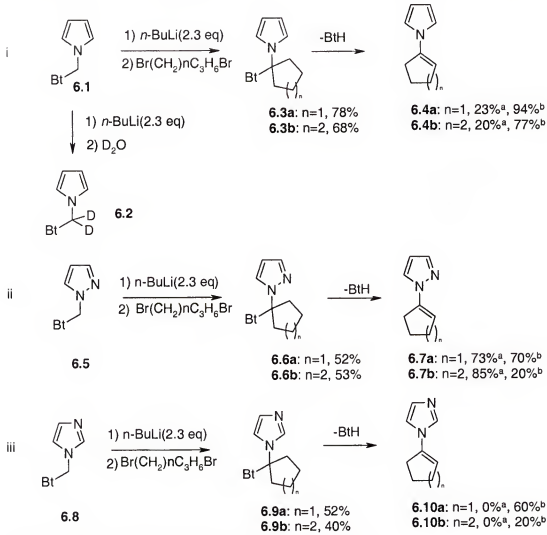


Scheme 6-3

6.2 Results and Discussion

Generation of geminal dianion equivalents and their reaction with dihaloalkanes. The dianion equivalent precursor *N*-(benzotriazol-1-ylmethyl) heterocycles were previously synthesized in our group [1989JHC829]. 1-(Imidazol-1-yl)methyl-5-phenyltetrazole (**6.12**) was synthesized by the reaction of imidazole with 1-chloromethyl-5-phenyltetrazole in the presence of sodium hydroxide in 77% yield; 1-(pyrazol-1-yl)methyl-5-phenyltetrazole (**6.14**) was prepared similarly (Scheme 6-5). The

corresponding geminal dianion was generated by treatment of *N*-(benzotriazol-1-ylmethyl)heterocycles **6.1**, **6.5**, **6.8**, **6.12** or **6.14** with 2.3 equivalents of *n*-BuLi in THF at –78 °C. The formation of the geminal dianion was confirmed by the deuteriation experiment. After the treatment of compound **6.1** with 2.3 equivalents of *n*-BuLi in THF at –78 °C for 1 h, excess D_2O was added to quench the reaction. The deuterated product **6.2** was obtained in 78% yield (Scheme 6-4, i). In the ^1H NMR spectrum of the product, no singlet around 6.60 ppm was observed. In ^{13}C NMR spectrum, the triplet signal for



a: yields obtained using method A; b: yields obtained using method B.

Scheme 6-4

CD_2 at 52.4 ppm indicated deuterium attachment.

Dihaloalkanes, as dielectrophiles, reacted with the dianions to give the ring systems. The 5- and 6-membered ring systems were obtained in good yields from the corresponding dianion precursors using 1,4-dibromobutane or 1,5-dibromopentane (Scheme 6-4). When 1,3-dibromopropane was reacted with the dianions, the desired products, 4-membered rings were obtained in less than 10% yield due to the high ring strain.

The structures of products are clearly characterized by ^1H, ^{13}C NMR and microanalysis. The ^1H NMR spectra of the cyclization products showed the absence of any singlet peak around 6.5 ppm that was ascribed to Bt$\underline{CH_2}$N in the precursor molecules. The expected four separate groups of peaks (for a 6-membered ring) or three groups of peaks (for a 5-membered ring) appear in the aliphatic region.

Synthesis of *N*-cycloalkenyl-pyrroles, -pyrazoles and –imidazoles. Two methods have been used in the present work for the removal of benzotriazole to form the *N*-cycloalkenyl-heterocycles. One is the Lewis acid promoted removal of the benzotriazolyl group (method A) [1998CRV409]. The other (method B) is using base/DMSO system to remove the benzotriazole or 5-phenyltetrazole (pKa = 4.54) based on their low pKa values.

Using the first approach, **6.7a** and **b** were obtained in 73% and 85% yields by heating of compounds **6.6a** and **6.6b**, respectively, with $ZnBr_2$ in toluene at 80 ^{0}C for 30 minutes (Scheme 6-4 ii). However, compounds **6.4a** and **6.4b** were obtained in only 23% and 20% yields using the same reaction system starting from compounds **6.3a** and **6.3b** (Scheme 6-4 i). Removal of benzotriazole from compound **6.9a**,**b** proved difficult.

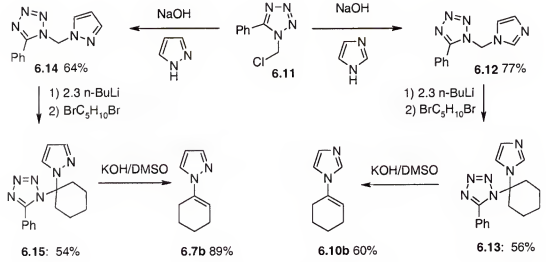
Heating of both **6.9a** and **6.9b** with $ZnBr_2$ under reflux in toluene up to 48 h did not give any desired product. According to the literature, benzotriazole group was removed with NaH from *N*-[(benzotriazol-1-yl)-3-butenyl]benzamide in refluxing toluene [1995JOC4002]. However, only the starting material was recovered after heating the compound **6.9b** and NaH in refluxing toluene for 18 h with or without $ZnBr_2$. Heating of **6.9b** and PhMgBr in toluene [1991HCA1924] or THF with or without $ZnBr_2$ for 18 h resulted in the recovery of the starting material.

Microwave irradiation was also used in order to promote elimination of BtH. Irradiation of **6.9b** with $ZnBr_2$ without solvent at 100 °C for 30 minutes gave no result. THF was used to repeat the reaction in vain at 67 °C and 100 °C. In toluene at 135 °C, a new spot was observed on TLC together with the starting material. After the purification, the new spot turned out to be 1-(cyclohex-1-enyl)benzotriazole. Raising the temperature to 150 °C led to tar formation. Under the above reaction conditions, imidazole turned out to be a better leaving group than benzotriazole. We turned our attention to compound **6.13** (Scheme 6-5) in which benzotriazole has been replaced with 5-phenyltetrazole, which was anticipated to be removed more easily than benzotriazole. Compound **6.13** was subjected to the conditions described above for compound **6.13** including the microwave irradiation. However, no desired *N*-cyclohexenyl-imidazole was detected.

Finally, heating compound **6.13** and 4 equivalents of KOH powder in DMSO at 130 °C for 3 hours (Method B) gave the desired product **6.10b** in 60% yield as yellow oil (Scheme 6-5). Compound **6.10a** was obtained in 60% yields from **6.9a** (Scheme 6-4, iii) with KOH/DMSO mixture at 130 °C for 3 hours as well. However, only about 20% of **6.10b** was obtained from **6.9b** with KOH/DMSO mixture, even after heating for up to 24

hour at 135 °C. As expected, the pyrrole products **6.4a**,**b** were given in 94% and 77% yields, respectively, in this KOH/DMSO mixture (Scheme 6-4, i). The pyrazole products **6.7a**,**b** were also formed under this reaction mixture but the yields were lower than that obtained in $ZnBr_2$/toluene system (Scheme 3, ii). However, **6.7b** was obtained in 89% yield from **6.15** in KOH/DMSO mixture (Scheme 6-5). The reasons for these variations in yields are unknown.

The structures of products were fully supported by their ^1H and ^{13}C NMR and microanalysis data. In the proton NMR spectrum of **6.4a**, a multiplet between 5.48 and 5.50 ppm was ascribed to the vinylic proton in the 5-membered ring. For **6.7a** and **6.10a**, a multiplet between 5.85 and 5.89 ppm and 5.65 and 5.68 ppm also confirmed the formation of the *N*-cyclopent-enylheterocycles. Similarly, a multiplet between 5.71 and 5.74 ppm in the ^1H NMR of **6.4b** was due to the vinylic proton in the 6-membered ring. For **6.7b** and **6.10b**, a multiplet between 6.10 and 6.13 ppm and 5.82 and 5.85 ppm also characterized the structures of *N*-cyclohexenyl-heterocycles.



Scheme 6-5

In summary, the generation of benzotriazole-stabilized geminal dianions has been established. The reactions of their dianions with dihaloalkanes gave 5- and 6-membered ring compounds in good yields. The benzotriazolyl or 5-phenyltetrazolyl groups in these compounds can be eliminated to give *N*-cycloalkenyl-azoles, a compound class previously rarely reported.

6.3 Experimental

General Comments. Melting points were determined on a MEL-TEMP® capillary melting point apparatus equipped with a Fluke 51 digital thermometer, and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, in $CDCl_3$ referenced to Me_4Si for the ^{1}H spectra and $CDCl_3$ for the ^{13}C spectra. Tetrahydrofuran was distilled under nitrogen from sodium-benzophenone immediately before use. All reactions with moisture-sensitive compounds were carried out in dry Argon atmosphere.

General procedure for the synthesis of compounds 6.3, 6.6, 6.9, 6.13 and 6.14. The corresponding dianion precursor (10 mmol) was dissolved in THF (180 mL) at –78 ^{0}C, *n*-BuLi (23 mmol, 14.4 mL, 1.6 M in hexane) was added drop wise. The resulting solution was stirred for 45-60 minutes. Then an appropriate dibromoalkane (1.2 equiv, 12.0 mmol) was added drop wise. The mixture was stirred overnight and allowed to come to rt. The reaction was quenched with 20 mL of water, and the layers were separated. The aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layer was dried over $MgSO_4$, and concentrated to give brown oil. The product was purified by column chromatography on silica gel.

1-[1-(1*H*-Pyrrol-1-yl)cyclopentyl]-1*H*-1,2,3-benzotriazole (6.3a): white prisms (78%) (from ethyl acetate/hexane), mp: 120–123 °C; ^{1}H NMR δ 1.93–1.98 (m, 4H), 2.73–2.82 (m, 2H), 3.11–3.20 (m, 2H), 6.20 (t, J = 2.1 Hz, 2H), 6.87 (t, J = 2.1 Hz, 2H), 6.90 (d, J = 5.4 Hz, 1H), 7.26–7.33 (m, 2H), 8.00–8.04 (m, 1H); ^{13}C NMR δ 22.2, 38.6, 85.3, 109.6, 110.8, 119.0, 119.9, 124.0, 127.5, 131.7, 146.8. Anal. Calcd for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.20. Found: C, 71.77; H, 6.81; N, 20.77.

1-[1-(1*H*-Pyrrol-1-yl)cyclohexyl]-1*H*-1,2,3-benzotriazole(6.3b): white crystals (68%) (from ethyl acetate/hexane), mp: 120–122 °C; ^{1}H NMR δ 1.56–174 (m, 4H), 1.78–1.90 (m, 2H), 2.60–2.75 (m, 2H), 2.98–3.06 (m, 2H), 6.28 (br s, 2H), 6.32 (d, J = 8.1 Hz, 1H), 6.95 (br s, 2H), 7.18–7.29 (m. 2H), 8.00 (d, J = 7.8 Hz, 1H); ^{13}C NMR δ 22.4, 24.6, 37.4, 78.5, 109.8, 110.9, 118.8, 119.7, 123.8, 127.5, 131.6, 146.2. Anal. Calcd for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04. Found: C, 71.77; H, 6.81; N, 20.77.

1-[1-(1*H*-Pyrazol-1-yl)cyclopentyl]-1*H*-1,2,3-benzotriazole (6.6a): white prisms (52%) (from ethyl acetate/hexane), mp: 119–121 °C; ^{1}H NMR δ 1.92–1.97 (m, 4H), 3.12–3.28 (m, 4H), 6.27 (t, J = 2.1 Hz, 1H), 7.30–7.38 (m, 2H), 7.40–7.48 (m, 2H), 7.52–7.58 (m, 1H), 7.98–8.03 (m, 1H); ^{13}C NMR δ 22.2, 37.8, 86.9, 107.6, 111.6, 119.9, 124.1, 127.5, 127.7, 131.8, 139.1, 146.8. Anal. Calcd for $C_{14}H_{15}N_5$: C, 66.38; H, 5.97; N, 27.65. Found: C, 66.32; H, 6.10; N, 27.66.

1-[1-(1*H*-Pyrazol-1-yl)cyclohexyl]-1*H*-1,2,3-benzotriazole (6.6b): white prisms (53%) (from ethyl acetate/hexane), mp: 149–151 °C; ^{1}H NMR δ 1.55–1.82 (m, 6H), 2.97–3.11 (m, 4H), 6.33 (t, J = 1.8 Hz, 1H), 7.07–7.11 (m, 1H), 7.26–7.31 (m, 2H), 7.51 (d, J = 2.4 Hz, 1H), 7.63 (br s, 1H), 7.98–8.03 (m, 1H); ^{13}C NMR δ 22.2, 24.6, 36.2, 80.3, 107.5, 111.6, 119.9, 123.9, 127.4, 127.5, 131.6, 139.3, 146.5. Anal. Calcd for

$C_{15}H_{17}N_5$: C, 67.39; H, 6.41; N, 26.20. Found: C, 67.43; H, 6.30; N, 26.43.

1-[1-(1*H*-Imidazol-1-yl)cyclopentyl]-1H-1,2,3-benzotriazole (6.9a): white prisms (52%) (from chloroform), mp:144–148 °C; ^{1}H NMR δ 1.94–2.04 (m, 4H), 2.78–2.90 (m, 2H), 3.18–3.28 (m, 2H), 7.00 (s, 1H), 7.04–7.14 (m, 2H), 7.32–7.40 (m, 2H), 7.81 (s, 1H), 8.02–8.10 (m, 1H); ^{13}C NMR δ 22.0, 38.4, 83.9, 110.3, 117.4, 120.4, 124.4, 128.1, 130.5, 131.3, 135.1, 147.0. Anal. Calcd for $C_{14}H_{15}N_5$: C, 66.38; H, 5.97; N, 27.65. Found: C, 66.34; H, 6.35; N, 27.50.

1-[1-(1*H*-Imidazol-1-yl)cyclohexyl]-1H-1,2,3-benzotriazole (6.9b): white prisms (40%) (from chloroform), mp:165–167 °C; ^{1}H NMR δ 1.60–1.90 (m, 6H), 2.62–2.74 (m, 2H), 3.12–3.24 (m, 2H), 6.76–6.84 (m, 1H), 7.00 (s, 1H), 7.10 (s, 1H), 7.29-7.36 (m, 2H), 7.86 (s, 1H), 8.02–8.10 (m, 1H); ^{13}C NMR δ 22.2, 24.4, 37.0, 77.6, 110.5, 116.8, 120.4, 124.3, 128.0, 130.4, 131.2, 134.9, 146.6. Anal. Calcd for $C_{15}H_{17}N_5$: C, 67.39; H, 6.41; N, 26.20. Found: C, 67.67; H, 6.59; N, 26.52.

1-[1-(1*H*-Imidazol-1-yl)cyclohexyl]-5-phenyl-1*H*-1,2,3,4-tetrazole (6.13): white needles (56%) (from chloroform), mp: 105–106 °C; ^{1}H NMR δ 1.40–1.90 (m, 6H), 2.62–2.76 (m, 2H), 3.20–3.54 (m, 2H), 7.04 (s, 1H), 7.19 (s, 1H), 7.44–7.54 (m, 3H), 7.88 (s, 1H), 8.08–8.18 (m, 2H); ^{13}C NMR δ 21.9, 24.1, 35.6, 78.1, 116.0, 126.9, 127.0, 128.9, 130.0, 130.6, 134.4, 165.1. Anal. Calcd for $C_{16}H_{18}N_6$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.14; H, 6.38; N, 28.43.

1-[1-(1*H*-Pyrazol-1-yl)cyclohexyl]-5-phenyl-1*H*-1,2,3,4-tetraazole (6.15): white prisms (54%) (ethyl acetate/hexane), mp: 111–113 °C; ^{1}H NMR δ 1.50–1.80 (m, 6H), 2.90–3.20 (m, 4H), 6.31 (br s, 1H), 7.40–7.48 (m, 3H), 7.56 (br s, 1H), 7.70–7.76 (m, 1H), 8.10–8.18 (m, 2H); ^{13}C NMR δ 22.0, 24.3, 35.1, 81.3, 106.9, 127.0, 127.2,

127.3, 128.8, 130.3, 140.2, 164.7. Anal. Calcd for $C_{16}H_{18}N_6$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.67; H, 6.03; N, 28.71.

Typical procedure for the synthesis of *N*-cycloalkenyl-azoles compounds.

Method A. 6.3a (0.25 g, 1 mmol) and $ZnBr_2$ (0.45 g, 2 mmol) were placed in a dry flask under argon, 5 mL toluene was added and heated at 80 °C for 45 min. The reaction mixture was then cooled to rt. and extracted with ethyl ether, dried ($MgSO_4$) and concentrated to give white solid, which was purified by column chromatography with hexane as eluent to give 30 mg of white powder.

Method B. Compound **6.3a** (0.10 g, 0.4 mmol) was dissolved in 5 mL of dry DMSO, KOH powder (0.5 g, 9 mmol) was added. The resulting mixture was heated at 110 °C for 3 h under nitrogen atmosphere with stirring. The reaction mixture was cooled to room temperature, extracted with ethyl ether; the organic layer was washed with water (5 x 5 mL), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure in ice-water bath. The product was purified by column chromatography on silica gel using 5% ethyl ether in pentane.

1-(1-Cyclopenten-1-yl)-1*H*-pyrrole (6.4a): white solid, mp: 32–34 °C; ^{1}H NMR δ 1.99–2.10 (m, 2H), 2.46–2.51 (m, 2H), 2.73–2.79 (m, 2H), 5.48–5.50 (m, 1H), 6.21 (t, J = 2.1 Hz, 2H), 6.91 (t, J = 2.1 Hz, 2H); ^{13}C NMR δ 22.0, 30.5, 31.8, 109.2, 109.3, 118.7, 140.1. Anal. Calcd for $C_9H_{11}N$: C, 81.16; H, 8.32; N, 10.52. Found: C, 80.98; H, 8.63; N, 10.39.

1-(1-Cyclohexen-1-yl)-1*H*-pyrrole (6.4b): colorless oil; ^{1}H NMR δ 1.61–1.69 (m, 2H), 1.77–1.85 (m, 2H), 2.14–2.21 (m, 2H), 2.42–2.47 (m, 2H), 5.71–5.74 (m, 1H), 6.18–6.20 (m, 2H), 6.88–6.90 (m, 2H); ^{13}C NMR δ 22.0, 22.6, 24.2, 27.1, 108.6, 112.7,

117.8, 136.2. Anal. Calcd for $C_{10}H_{13}N$: H, 9.34; N, 9.51. Found: C, 80.98; H, 8.45; N, 9.41. HRMS Calcd for $C_{13}H_{13}N$ (M): 147.1048. Found: 147.1087.

1-(1- Cyclopenten-1-yl)-1*H*-pyrazole (6.7a): Lit. [1970JOC3459] colorless oil; ^{1}H NMR δ 2.04–2.14 (m, 2H), 2.50–2.58 (m, 2H), 2.83–2.91 (m, 2H), 5.85–5.89 (m, 1H), 6.32–6.33 (m, 1H), 7.59 (br d, J = 2.7 Hz, 1H), 7.60 (d, J = 1.8 Hz, 1H); ^{13}C NMR δ 22.1, 30.7, 31.4, 106.3, 112.3, 127.2, 140.3, 140.4.

1-(1-Cyclohexen-1-yl)-1*H*-pyrazole (6.7b): Lit. [1970JOC3459] colorless oil; ^{1}H NMR δ 1.63–1.71 (m, 2H), 1.80–1.88 (m, 2H), 2.19–2.26 (m, 2H), 2.55–2.61 (m, 2H), 6.10–6.13 (m, 1H), 6.30–6.31 (m, 1H), 7.58 (br d, J = 1.8 Hz, 1H), 7.61 (dd, J = 2.4, 0.6 Hz, 1H); ^{13}C NMR δ 21.9, 22.4, 24.0, 26.0, 105.8, 113.9, 125.8, 136.5, 139.6.

1-(1-Cyclopenten-1-yl)-1*H*-imidazole (6.10a): off-white prisms (ethyl acetate/hexane), mp: 40–42 °C; ^{1}H NMR δ 2.04–2.14 (m, 2H), 2.48–2.55 (m, 2H), 2.74–2.81 (m, 2H), 5.65–5.68 (s, 1H), 7.08 (br s, 1H), 7.14–7.16 (m, 1H), 7.67 (br s, 1H); ^{13}C NMR δ 21.8, 30.4, 31.6, 113.3, 116.9, 129.6, 135.0, 136.9. HRMS Calcd for $C_8H_{10}N_2$ (M): 134.0844. Found: 134.0856.

1-(1-Cyclohexen-1-yl)-1*H*-imidazole (6.10b) Lit [1979TL5011]**:** brown oil (60%); ^{1}H NMR δ 1.65–1.71 (m, 2H), 1.78–1.86 (m, 2H), 2.18–2.22 (m, 2H), 2.40–2.44 (m, 2H), 5.82–5.85 (m, 1H), 7.08 (s, 1H), 7.09 (s, 1H), 7.67 (s, 1H); ^{13}C NMR δ 21.4, 22.1, 23.8, 27.1, 116.2, 116.4, 129.0, 133.5, 134.2.

General procedure for the synthesis of compounds 6.12 and 6.14

[1989JHC829]**:** Heterocycle (20 mmol) and NaOH powder (1.6 g, 40 mmol) were dissolved in DMSO (20 mL, dried over molecular sieves) and heated at 60 °C for 30 minutes, then 1-Chloromethyl-5-phenyltetrazole (3.8 g, 20 mmol) added in one portion

and heated at 60 °C for 1 h. The reaction mixture was cooled to room temperature, and poured onto 100 g of ice in a beaker with rapid stirring. After 10 minutes, white precipitates were filtered off and washed with cold water (100 mL). The product was purified via recrystallization.

1-(1*H*-Imidazol-1-ylmethyl)-5-phenyl-1*H*-1,2,3,4-tetrazole (6.12): brown prisms (77%) (ethyl acetate/hexane), mp: 123–125 °C; ^{1}H NMR δ6.65 (s, 2H), 7.11 (s, 1H), 7.24 (s, 1H), 7.45–7.54 (m, 3H), 7.87 (s, 1H), 8.12–8.18 (m, 2H); ^{13}C NMR δ60.3, 118.9, 126.4, 127.0, 128.9, 130.9, 131.0, 137.4, 166.2. Anal. Calcd for $C_{11}H_{10}N_6$: C, 58.40; H, 4.46; N, 37.15. Found: C, 58.69; H, 4.66; N, 37.03.

1-(1*H*-Pyrazol-1-ylmethyl)-5-phenyl-1*H*-1,2,3,4-tetrazole (6.14): white needle (64%) (ethyl acetate/hexane), mp: 115–116 °C; ^{1}H NMR δ6.36–6.40 (m, 1H), 6.82 (s, 2H), 7.42–7.52 (m, 3H), 7.59–7.62 (m, 1H), 7.78–7.82 (m, 1H), 8.15–8.18 (m, 2H); ^{13}C NMR δ65.0, 108.1, 127.0, 128,8, 130.30, 130.6, 141.9, 164.7. Anal. Calcd for $C_{11}H_{10}N_6$: C, 58.40; H, 4.46; N, 37.15. Found: C, 58.60; H, 4.40; N, 37.02.

CHAPTER 7
SUMMARY AND CONCLUSIONS

As mentioned in the introduction, heterocycles are indispensable for modern life and the society, and new methods for more efficient preparations will help improve living conditions on this planet. The present thesis has helped expanding the knowledge in the following way. A study of the application of benzotriazole as a useful synthetic auxiliary and for the further understanding of its chemistry has been carried out. Several types of benzotriazole-substituted intermediates have been made, and their utility in a variety of synthetic transformations have been explored.

Classical chemical syntheses from "*n*" starting materials require sequences of at least "*n*-1" preparation steps including separation and purification of the intermediates. A perfect alternative for the rapid syntheses of a large variety of agrochemically and pharmaceutically relevant products is one-pot syntheses by multicomponent reactions. As mentioned in the introduction, chemical properties of benzotriazole allow for one-pot synthesis of versatile reactive intermediates *via* multicomponent condensation reactions. Thus, in Chapter 2, a three component condensation reaction of benzotriazole, ammonia and aromatic aldehydes is described, which provided a convenient source of 1,3-dipole precursors, *N*-arylmethylene[(benzotriazol-1-yl)arylmethyl]amines [1991S863]. 1,3-Dipolar cycloaddition reactions are important in the synthesis of a variety of 5-membered heterocycles. We used these 1,3-dipole precursors to develop a practical and convenient synthesis of 5-arylamino-2,4-diarylthiazoles in moderate-to- good yields. Thiazoles

constitute a group of heterocycles of increasing interest and application in medicinal chemistry. Compounds containing thiazole ring have been reported to have diverse biological activities, and have been used in clinical trials. Synthetic antibiotic cefotaxime has a thiazole ring in the molecule [1997MI147]. Several substituted aminothiazoles are reported to possess anti-inflammatory, or antioxidant activities [1998AF263]. Diarylthiazoles functionalized at 2 and 4 positions, including 2,4-bis(3-indolyl)thiazoles are reported to be potent cytotoxic reagents [1999BML569]. However, there are only a few reports on the synthesis of 2,4-diarylthiazoles functionalized at the 5 position [1972HCA916], [1974CH810]. Our methodology should provide convenient access to many other derivatives of 5-arylamino-2,4-diarylthiazoles that have potential biological activities.

Three component condensation reactions of benzotriazole, 3-phenylpropylamine and aldehydes also gave us quick access to important intermediates such as *N,N*-bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)-3-phenyl-1-propanamine, 3-(1*H*-1,2,3-benzotriazol-1-yl)-2-(3-phenylpropyl)-1-isoindolinone, and 5-(benzotriazolyl)-2-(3-phenylpropyl)-2-pyrrolidinone, as described in Chapter 5. Cyclization of these compounds in the presence of Lewis acids afforded 2-benzazepine derivatives and the related fused ring heterocycles in one step. A series of *N*-substituted 2-benzazepines were obtained by nucleophilic substitution of benzotriazolyl moiety in 2-(benzotriazolylmethyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine using different nucleophiles. 2-Benzazepine derivatives are of considerable medicinal interest. This new approach uses mild reaction conditions and simple reaction procedures, and provides alternative pathway for the synthesis of variety of 2-benzazepine analogues with potential pharmacological properties.

Benzotriazole is a very good leaving group when there is α heteroatom (N, S, or O) in the molecule. However, when there is no heteroatom at the α position, benzotriazole is not a good leaving group. This limits the utility of benzotriazole as a synthetic auxiliary to some extent. We have attempted to convert benzotriazole into the corresponding *N*-oxide, and study the properties of the oxidized benzotriazole group as a nucleofuge. We studied the direct oxidation of 1-and 2-alkylbenzotriazoles and 1-(benzotriazol-1-yl)alkenes using dichloromethane solution of dimethyldioxirane (DMD) in Chapter 3 and Chapter 4. We have developed a highly efficient synthetic pathway to oxidize 1-alkylbenzotriazoles into 3-alkylbenzotriazole 1-oxides by using DMD. Conversion of benzotriazole into the corresponding *N*-oxide, however, does not increase its nucleofugacity enough to displace it with nucleophiles. We also studied the other properties of 3-alkylbenzotriazole 1-oxides. Position 7 in 3-alkylbenzotriazole 1-oxides is activated towards proton loss in the presence of a strong base. The oxygen atom in 3-alkylbenzotriazole 1-oxides can be silylated to form trimethylsilyloxy-benzotriazolium salts or removed by refluxing with acetic anhydride. Dimethyldioxirane reacts with 2-alkylbenzotriazoles entirely differently, and converts them into 2-alkyl-*trans*-4,5,6,7-diepoxy-4,5,6,7-tetrahydrobenzotriazoles.

Dimethyldioxirane reacts differently with 1-(benzotriazol-1-yl)alkenes than with 1- and 2-alkylbenzotriazoles. In Chapter 4, we showed that dimethyldioxirane converts of 1- and 2-substituted 1-(benzotriazol-1-yl)alkenes into the corresponding epoxides in almost quantitative yields. The rate of epoxidation decreases for alkenes with electron-withdrawing substituents. Epoxides are important reactive intermediates in organic chemistry. We showed that benzotriazole group effectively stabilizes oxiranyl anion at

temperatures below –116 °C, thus allowing various functionalization of the epoxides.

Geminal dianions are important reactive species, which can be obtained easily when electron-withdrawing groups are present in the molecule. In Chapter 6, we studied the generation of benzotriazole-stabilized geminal dianions. Both the benzotriazolyl and 5-phenyltetrazolyl groups can stabilize geminal dianions. The reactions of dianions with dihaloalkanes gave 5- and 6-membered ring compounds in good yields. Both benzotriazolyl and 5-phenyltetrazolyl groups in these compounds can be eliminated using two different procedures to give *N*-cycloalkenyl-pyrroles, -pyrazoles and -imidazoles, examples of a compound class previously rarely reported.

Thus, the properties of benzotriazolyl group have been further explored, and a greater understanding of benzotriazole chemistry thereby resulted. The results described above further illustrate the synthetic potential of benzotriazole-substituted intermediates, particularly in the synthesis of novel heterocyclic compounds. Heterocycles are chemically more flexible and better able to respond to the many demands of biochemical systems. There is no doubt that benzotriazole as a vehicle in the synthesis of organic compounds, will continue to show its magic in synthetic method-developments for various heterocycles.

REFERENCES

The reference citation system used throughout this dissertation is that found in Comprehensive Heterocyclic Chemistry, edited by Alan R. Katritzky and Charles W. Rees, Pergamon Press, Oxford, 1984. Each time a reference is cited, a code appear in bracket in the form [####ABC####]. The first four digits denote the year of the journal, the letter code represents the title of the journal or book and the latter digits indicate the page of the journal or book on which the article begins.

Additional notes:

1. References are listed a) chronologically by year, b) alphabetically by letter code, c) page numbers.
2. Each reference code is followed by the complete literature citation in the ACS format.
3. Books and patents are given the letter code "MI".

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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